

Exhibit B

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EXHIBIT 1

**The Parties Where Volunteers Pack
Abortion Pills for Red-State Women
- WSJ**

<https://www.wsj.com/us-news/abortion-pill-parties-shipping-148e3c15>

The Parties Where Volunteers Pack Abortion Pills for Red-State Women

Amid risks, volunteers are mobilizing to assist networks that mail abortion medication to women in states with strict limits

By Scott Calvert [Follow](#) | Photographs by Kayana Szymczak for WSJ

Aug. 12, 2024 9:00 pm ET

SOMERVILLE, Mass.—The women huddling around the conference table shuttled the small cardboard boxes along, assembly-line style. Into each went medical-information paperwork and a handwritten note proclaiming, “We wish you the best!” Then came the critical addition, a two-drug regimen that ends a pregnancy.

This tiny Boston-area office represents a new bulwark in America’s abortion battle. Volunteers are mobilizing with growing frequency for pill-packing parties to help strangers in faraway states circumvent strict laws. On a recent Monday evening, the group filled 350 boxes—in-home abortion kits ready for mailing to women in states such as Texas and Florida with near-total or six-week abortion bans.

Melissa Fischer, a 57-year-old internist, sees these efforts as a way to assist people tripped up by geography. “I strongly believe where somebody lives shouldn’t dictate their access to critical healthcare,” she said.

Retirees and professionals ate pizza, sipped Chardonnay in red plastic cups and chatted while working purposefully. Many portray the sessions as a tangible way to push back against the 2022 Supreme Court ruling that eliminated a constitutional right to abortion.

“It’s a little bit of an antidote to hopelessness,” said Judy Fleishman, 70, a medical educator. “There’s something you can do.”



Women prepare in-home abortion kits at a ‘pill-packing party’ at the MAP’s offices.

Growing urgency

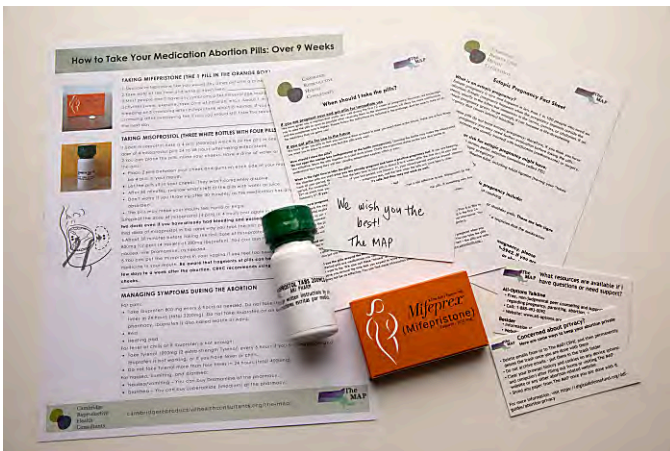
The parties support the Massachusetts Medication Abortion Access Project, also known as the MAP, part of a growing movement to send abortion pills into ban states, often for just a few dollars. The nearly year-old MAP, like similar programs, leverages a state shield law meant to protect clinicians from legal jeopardy, including extradition. Massachusetts is among eight states with such laws.

These operations are intensifying amid more heated political debates. Vice President Kamala Harris is spotlighting abortion rights in her presidential bid, while Republicans struggle to articulate a winning message.

From July 2023 to March, shield-law groups provided more than 68,000 abortion kits by mail to residents in states with tight limits on the procedure or telemedicine, according to WeCount, an abortion-data project sponsored by the Society of Family Planning, which backs abortion rights.

Shield-law providers accounted for about 9,500 medication abortions in March, up from 5,620 in July 2023, WeCount says.

"I think as long as we see states that are passing more and more restrictions, we're going to see these numbers continue to grow," said WeCount co-chair Ushma Upadhyay, a professor at the University of California at San Francisco.



Patient packages include two abortion medications, instructions and additional information.

Abortions reached nearly 100,000 nationwide in March, up from 84,000 in May 2022, according to WeCount, despite 18 states imposing near-total or six-week bans. Medication abortions now outnumber surgical procedures. Nearly 20% of all abortions are via drugs sent by mail, including from bricks-and-mortar clinics.

So far, efforts targeting telemedicine abortions have failed. The Supreme Court in June rejected a bid to restrict access to mifepristone, one of the two abortion drugs. Some Republicans in Congress, including vice presidential nominee JD Vance, have called for enforcing the 1873 Comstock Act, a federal law barring the shipping of abortion drugs. More recently Vance has said the issue should be left to states.

Risk and pushback

App. 000003



MAP co-founder Angel Foster said the pill-packing parties are essential to its operations.

Still, legal experts say there are risks for those involved in mailing pills to states with bans.

Angel Foster, 50, a doctor who helped launch the MAP last fall, trusts the Massachusetts shield law. But because it doesn't apply in other states, she won't visit her mother and stepfather in South Carolina and avoids flights that require stopovers in Texas.

Maureen Paul, the MAP's medical director, doesn't feel safe visiting her brother in Florida, where a six-week ban took effect in May. "We are no strangers to risk. I've had my home picketed, I've had death threats," she said. "But we're not fearful, we're not paralyzed. We're determined to act."

Frustrated officials in states with stringent laws can't disrupt the mail, but some are warning providers. Arkansas Attorney General Tim Griffin, a Republican, demanded two entities in May stop helping state residents get the pills, asserting such actions violate Arkansas law.

One warning went to Choices Women's Medical Center in New York, which doesn't mail pills but removed from its website wording about Arkansans taking clinic-provided pills at home. Founder Merle Hoffman said she thinks Griffin misunderstood how her clinic operates. A cease-and-desist letter also went to Aid Access, the largest shield-law provider, which disputes the allegations.



The Massachusetts Medication Abortion Access Project's office in Somerville, Mass.

Antiabortion groups say it is dangerous for women to take these pills without medical supervision. Providers say it's safe and that they screen for potential problems.

Pill-mailers are in new legal terrain. "No one has challenged any of these laws yet," said Rachel Rebouché, dean of the Temple University Beasley School of Law. "Texas has not tried to prosecute [clinicians], they haven't been sued, a medical board hasn't tried to discipline them. That's not to say those things aren't possible."

In Massachusetts, Paul, a 74-year-old doctor, is one of four prescribers at the MAP. In 1968, pregnant at age 18, she couldn't get a hospital abortion and feared seeking an illegal one. She carried to term and gave up her child for adoption, an experience she calls "deeply traumatic and defining."

Launched last fall, the MAP is a project of Cambridge Reproductive Health Consultants, a nonprofit co-founded by Foster that has worked to boost medication abortion access in countries including Thailand, Pakistan and Uganda—and saw a need for similar work in the U.S. MAP harnesses websites like plancpills.org to get the word out to women nationwide. Prospective patients fill out intake forms online and mainly correspond by email, although some talk by phone with Foster or a prescriber.

The program accepts patients up to the 11th week of pregnancy, aiming to get pills to them by 12 weeks. Most are earlier than nine weeks, Foster said. Despite a \$250 list price, patients pay about \$130 on average; a third pay \$25 or less.

The 6 p.m. party



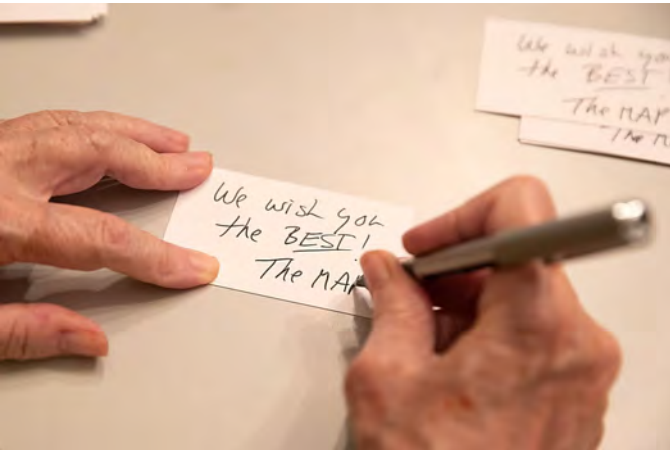
Tote bags containing the MAP's patient packages are carried to a post office for mailing.

At the MAP's office, before the recent pill-packing party, Foster read aloud comments women shared on intake forms. A Nebraska mother wrote: "I was using protection, but it failed, and I cannot afford to have another child right now." A Florida woman with a diabetic 5-year-old said: "I am struggling to pay my bills, and I'm not mentally ready to bring another child into my life yet."

Nearby, a MAP staffer printed address labels for 45 boxes of pills before packing them into tote bags for the trip to the post office. They were bound for 19 states, including Texas, Georgia and Florida.

Around 6 p.m., the volunteers filed in from work or home to replenish the supply of preloaded boxes. The gatherings jumped from monthly to twice-monthly in July, the MAP's busiest month with 560 boxes shipped, and are set to go weekly this fall.

Sonia Dettmann, 81, a retired clinical social worker, hasn't missed any. "I feel that abortion care is healthcare, and this is one way of supporting healthcare for folks from states where abortion is banned. It's that simple," she said as she dropped mifepristone cartons into each box.



A handwritten card is included with each MAP package.

Another regular, Erin Gately, 47, likes to write notes in gold ink for "a little extra touch." An OB-GYN nurse practitioner, she sees "the challenges that come with an unplanned pregnancy and, whether somebody decides to continue with that unplanned pregnancy or not, it's their choice."

As boxes circulated around the table, conversation pinged from the Paris Olympics to a promising birth-control gel for men. Amid upbeat banter, the crew kept their production line humming. Though they fell short of Foster's

App. 000006

goal of packing 475 boxes, she assured them 350 was more than fine.

“I am very impressed with us,” she said.

Write to Scott Calvert at scott.calvert@wsj.com

Appeared in the August 13, 2024, print edition as 'Abortion Fight Has New Front: Pill Parties'.

EXHIBIT 2

**FDA, Center for Drug Evaluation and Research,
Summary Review of 020687Orig1s020**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

1. Introduction
2. Background
3. CMC
4. Nonclinical Pharmacology/Toxicology
5. Clinical Pharmacology
6. Clinical Microbiology
7. Efficacy/Statistics
8. Safety
9. Advisory Committee Meeting
10. Pediatrics
11. Other Relevant Regulatory Issues
12. Labeling
13. Decision/Action/Risk Benefit Assessment

1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
 - Day One: Mifeprex Administration (oral)
One 200 mg tablet of Mifeprex is taken in a single oral dose
 - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)
Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route
2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of “physician” to “healthcare provider” in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation.”
10. Removal of references to “under Federal law” from the Prescriber’s Agreement under the REMS

11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

Comment: On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.

6. Clinical Microbiology

Not applicable.

7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
 - a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
 - b. Allowing home administration of misoprostol
 - c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprax orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprax administration:*
The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.
2. *Support for extending the gestational age to 70 days:*
The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012¹, Boersma et al², Sanhueza Smith et al³) and one randomized controlled trial (RCT) (Olavarrieta et al⁴) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin⁵ covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond⁶ of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses \geq 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

¹ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

² Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

³ Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015; 22: 75-82

⁴ Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. *Bull World Health Organ* 2015; 93: 249-258

⁵ Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion *Obstet Gynecol*: a Systematic Review. *Obstet Gynecol* 2015; 126(1): 12-21

⁶ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al⁷ evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review⁸ of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al⁹) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.
4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

⁷ Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. *Contraception* 2010; 81(4): 269-74. doi: 10.1016/j.contraception.2009.09.007. Epub Oct 29, 2009

⁸ Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004; 103: 851-859

⁹ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

- Winikoff et al¹⁰ – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin¹¹ – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al¹² – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al¹³ – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al¹⁴ – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al¹⁵ – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

¹⁰ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

¹¹ Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004; 103: 851-859

¹² Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

¹³ Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. *Eur J Contracept Reprod Health Care* 2014; 19(6): 457-464

¹⁴ Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012; 86: 251-256

¹⁵ Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310

Raymond¹⁶. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposed dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al¹⁷ that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

Conclusions: I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

Comment: Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4)

(b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

¹⁶Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.

¹⁷Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet* 2011; 377: 1155-61.

8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

Exposure: Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

Deaths: Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al¹⁸) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al¹⁹) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

Nonfatal serious adverse events: The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

¹⁸Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

¹⁹Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. *Med J Austral* 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al²⁰ reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al²¹) reported one ectopic among 847 women (0.12%).

Comment: The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)²² in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission- specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

Loss to follow-up: The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al²³) to 22% in the Grossman et al²⁴ study using telemedicine to deliver medical

²⁰Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015;125(1):175-183.

²¹Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008;112(6):1303-1310.

²²Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012;120:1070-6.

²³Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. *Obstet Gynecol* 2014;123:88-95.

²⁴Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

abortion services.

Comment: Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

Common adverse events: The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

Table 1: Common Adverse Events ($\geq 15\%$) in U.S. Studies of the Proposed Dosing Regimen

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

Source: Data from Middleton²⁵, Winikoff²⁶ and Winikoff²⁷ as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al²⁸ and Gatter et al²⁹) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

²⁵ Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005; 72: 328-32

²⁶ Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

²⁷ Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310

²⁸ Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015;22:75-82.

²⁹ Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

Comment: While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

Postmarketing experience – Spontaneous reports:

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

Submission-specific safety issues:

- Anaphylaxis/angioedema: The (b) (6) (b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

Comment: (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- Uterine rupture: As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) (b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.

Published literature reported three case reports^{30,31,32} of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

Comment: I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

³⁰Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. *Journal of Obstet Gynaecol* 2007; 27: 869-870

³¹ Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus *J Obstet Gynaecol* 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

³² Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. *BJOG* 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- Changing the timing interval between Mifeprax and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al³³. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.
- Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al³⁴ and Ireland et al³⁵. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.
- Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al³⁶) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

³³ Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. *Obstet Gynecol* 2013;121(6):1335-1347.

³⁴ Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

³⁵ Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015;126:22-8.

³⁶ Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al³⁷ also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al³⁸ that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article³⁹ that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.
- *Allowing providers other than physicians to provide Mifeprex:* The current Prescriber's Agreement in the REMS specifies that "...Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications..." In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

³⁷ Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. *Contraception* 2006;74:36-41.

³⁸ Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? *Contraception* 2015;91:6-11.

³⁹ Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

currently providing abortion services. One of these studies (Kopp Kallner et al⁴⁰) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were $\geq 96\%$ regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, $p=0.14$). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term “healthcare provider who prescribes” would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen. No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

⁴⁰ Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. *Human Reprod* 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al⁴¹). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al⁴²)

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al⁴³ study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter⁴⁴ et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al⁴⁵ evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

⁴¹Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

⁴² Ibid.

⁴³Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

⁴⁴Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

⁴⁵Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

- Niinimaki et al⁴⁶ used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women \geq age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al⁴⁷ study. (b) (6), (b) (4)

Supportive data from a Finnish registry (Niinimaki et al) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

11. Other Relevant Regulatory Issues

(b) (6)

(b) (6) reviewed the Medication Guide in conjunction with the (b) (6) (b) (6). Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

⁴⁶Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

⁴⁷Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

⁴⁸Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

(b) (6) (b) (6)

(u) (o) reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6). After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

(b) (6) (b) (6)

(b) (6) (b) (6) in the (b) (6) (b) (6) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term "under Federal law" from the Prescriber's Agreement.
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant's proposed terminology of (b) (4) is too broad and that a more appropriate description is "healthcare provider who prescribes," which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex.
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with other REMS programs. References to "physician" should be changed to "healthcare provider who prescribes."
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
 1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
 2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
 3. The Prescriber's Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
 4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

12. Labeling

Carton and container labeling was reviewed by the [REDACTED] (b) (6)
[REDACTED] (b) (6) the [REDACTED] (b) (6) (b) (6)
and the [REDACTED] (b) (6) (b) (6) Their
comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported. Agreement on labeling was reached on March 29, 2016.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

Postmarketing Requirements/Postmarketing Commitments: None.

Risk Evaluation and Mitigation Strategies (REMS): The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase “Under Federal law” from the Prescriber’s Agreement
6. Replacing the term “licensed physician” with “healthcare provider who prescribes”

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6) (b) (6).

The (b) (6) concurred with conforming changes to the Prescriber’s Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term “under Federal law”. A rationale for the original inclusion of the phrase “Under Federal law” cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber’s Agreement.

The (b) (6) concurred with use of the term “healthcare providers who prescribe.” To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams’ recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team’s rationale for this modification was needed. The review team’s rationale for this change was:

APPEARS THIS WAY ON ORIGINAL

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

13. Decision/Action/Risk Benefit Assessment

Decision:

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

Benefit Risk Assessment:

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow-up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.
2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.
3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.
4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and the (b) (6) (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through the (b) (6) (6)).

Therefore, the Patient Agreement Form will be retained and other changes will be made in the REMS to reflect that it is being retained.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

EXHIBIT 3

FDA, Center for Drug Evaluation and Research, Mifepristone Summary Review 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020687Orig1s025

Trade Name: Mifeprex Tablets 200 mg

Generic or Proper Name: Mifepristone

Sponsor: Danco Laboratories, LLC

Approval Date: January 3, 2023

Indication: For modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program.

CENTER FOR DRUG EVALUATION AND RESEARCH**020687Orig1s025****CONTENTS****Reviews / Information Included in this NDA Review.**

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	X
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

APPROVAL LETTER



NDA 020687/S-025

SUPPLEMENT APPROVAL

Danco Laboratories, LLC

(b) (4), (b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6) :

Please refer to your supplemental new drug application (sNDA) dated and received June 22, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets, 200 mg.

This Prior Approval sNDA provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed our review of the supplemental application, as amended. It is approved effective the date of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Mifepristone REMS Program, of which Mifeprex is a member, was originally approved on April 11, 2019, and the most recent REMS modification was approved on May 14, 2021. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Mifeprex outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.
- Replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- Additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

Your proposed modified REMS, received on June 22, 2022, amended and appended to this letter, is approved. The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

This shared system REMS, known as the Mifepristone REMS Program, currently includes those products listed on the FDA REMS website³.

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the approval of the modified SSS REMS (1/3/2023) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification Statistics

a. Prescribers

- Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
- Number and percentage of newly certified prescribers
- Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

b. Pharmacies

³ <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>

- i. Number of certified pharmacies
 - ii. Number and percentage of newly certified pharmacies
 - iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
 - c. Wholesalers/Distributors
 - i. Number of authorized wholesalers/distributors
 - ii. Number and percentage of newly authorized wholesalers/distributors
 - iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)
2. Utilization Data
- a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
 - b. Number of prescriptions dispensed from pharmacies
3. REMS Compliance Data
- a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
 - i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
 - ii. The number of audits expected, and the number of audits performed
 - iii. The number and type of deficiencies noted
 - iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
 - v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)
 - vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)
 - b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
 - i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
 - ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
 - 1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
 - 2. The source of the non-compliance data (e.g., self-reported, audit, other)
 - 3. A root cause analysis of the non-compliance

4. Actions to prevent future occurrences and outcomes of such actions
- iii. Prescriber compliance
 1. Number and percentage of certified prescribers who became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
- iv. Pharmacy compliance
 1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
 2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
 3. Number and percentage of pharmacies that became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
- v. Wholesaler/distributor compliance
 1. Number of healthcare providers who successfully ordered mifepristone who were not certified
 2. Number of non-certified pharmacies that successfully ordered mifepristone
 3. Number of shipments sent to non-certified prescriber receiving locations
 4. Number of shipments sent to non-certified pharmacy receiving locations
 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively,

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

App. 000046

updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT METHODOLOGY

(insert concise description of content in bold capital letters, e.g.,

ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 020687/S-000/
PRIOR APPROVAL SUPPLEMENT**

**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call  (b) (6)

Sincerely,

{See appended electronic signature page}

 (b) (6)

Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
 - REMS Document
 - Prescriber Agreement
 - Patient Agreement Form
 - Pharmacy Agreement Form

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning. Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3).

Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

INDICATIONS AND USAGE

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

DOSAGE AND ADMINISTRATION

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

CONTRAINDICATIONS

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

WARNINGS AND PRECAUTIONS

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

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FULL PRESCRIBING INFORMATION**WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING**

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis [see *Warnings and Precautions* (5.1)].
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding [see *Warnings and Precautions* (5.2)].

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program [see *Warnings and Precautions* (5.3)].

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION**2.1 Dosing Regimen**

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

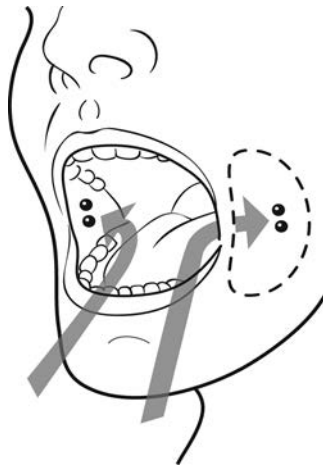
Remove any intrauterine device ("IUD") before treatment with MIFEPREX begins [see *Contraindications* (4)].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
 - *Day One:* MIFEPREX Administration
One 200 mg tablet of MIFEPREX is taken in a single oral dose.
 - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

Figure 1



2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol [see *Clinical Studies (14)*], discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms [see *Adverse Reactions (6)*].

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion [see *Use in Specific Populations* (8.1)]. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with "MF."

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any of the following conditions:
 - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) [see *Warnings and Precautions* (5.4)]
 - Chronic adrenal failure (risk of acute adrenal insufficiency)
 - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
 - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported [see *Adverse Reactions* (6.2)])
 - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

- Inherited porphyrias (risk of worsening or of precipitation of attacks)
- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device (“IUD”) in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX [see *Boxed Warning*]. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion [see *Boxed Warning*].

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the mifepristone REMS Program, because of the risks of serious complications [see *Warnings and Precautions* (5.1, 5.2)].

Notable requirements of the mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies [see *Contraindications* (4)]. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis [see *Warnings and Precautions* (5.1)]
- Uterine bleeding [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period [see *Warnings and Precautions* (5.2)].

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and
Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported

* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)

Blood and the lymphatic system disorders: anemia

Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)

Psychiatric disorders: anxiety

Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)

Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness

Respiratory, thoracic and mediastinal disorders: shortness of breath

Gastrointestinal disorders: dyspepsia

Musculoskeletal, connective tissue and bone disorders: back pain, leg pain

Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea

General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment [see *Dosage and Administration (2.3)*] to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

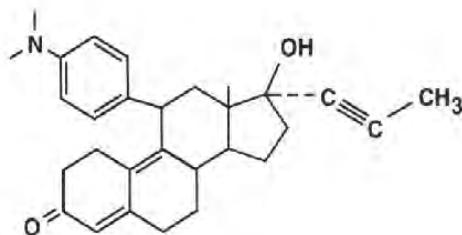
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11 β -[p-(Dimethylamino)phenyl]-17 β -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C₂₉H₃₅NO₂. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for C_{max} after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean C_{max} was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean AUC_{0-∞} was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1 -acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pombe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal)
Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%
<p>* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.</p> <p>** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.</p>		

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and
Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)].

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see *Warnings and Precautions* (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see *Warnings and Precautions* (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)]. Under the mifepristone REMS Program:
 - Patients must sign a Patient Agreement Form.
 - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever [see *Boxed Warning*].
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to 14 days after taking MIFEPREX [see *Dosage and Administration* (2.3)].
- Explain that
 - prolonged heavy vaginal bleeding is not proof of a complete abortion,
 - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
 - it is recommended that ongoing pregnancy be managed by surgical termination [see *Dosage and Administration* (2.3)]. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

01/2023

MEDICATION GUIDE**Mifeprex** (MIF-eh-prex) (mifepristone tablets, for oral use)

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:**Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally****Day 1:**

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See “What is the most important information I should know about Mifeprex?”

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See “How should I take Mifeprex?” for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to 16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 01/2023

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s025

REMS

Initial Shared System REMS approval: 04/2019

Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg

Progestin Antagonist

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG**

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
 - a. To become specially certified to prescribe mifepristone, healthcare providers must:
 - i. Review the Prescribing Information for mifepristone.
 - ii. Complete a *Prescriber Agreement Form*. By signing¹ a *Prescriber Agreement Form*, prescribers agree that:
 - 1) They have the following qualifications:
 - a) Ability to assess the duration of pregnancy accurately
 - b) Ability to diagnose ectopic pregnancies
 - c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
 - 2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
 - b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
 - i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
 - ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form*.

¹ In this REMS, the terms “sign” and “signature” include electronic signatures.

- iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
 - iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
 - v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.
 - vi. If mifepristone will be dispensed by a certified pharmacy:
 - 1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.
 - 2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
 - 3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.
 - vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:
 - 1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.
 - 2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.
 - 3) Ensure that healthcare providers under their supervision follow guidelines i.-v.
 - c. Mifepristone Sponsors must:
 - i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.
 - ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:
 - 1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.
 - 2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.
 - iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.
 - iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.
 - v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.
- The following materials are part of the Mifepristone REMS Program:
- *Prescriber Agreement Form for Danco Laboratories, LLC*
 - *Prescriber Agreement Form for GenBioPro, Inc.*
 - *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
 - a. To become specially certified to dispense mifepristone, pharmacies must:
 - i. Be able to receive *Prescriber Agreement Forms* by email and fax.
 - ii. Be able to ship mifepristone using a shipping service that provides tracking information.
 - iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
 - iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
 - 1) Review the Prescribing Information for mifepristone.
 - 2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
 - a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
 - b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
 - c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
 - e) Track and verify receipt of each shipment of mifepristone.
 - f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
 - g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - i) Maintain records of *Prescriber Agreement Forms*.
 - j) Maintain records of dispensing and shipping.
 - k) Maintain records of all processes and procedures including compliance with those processes and procedures.
 - l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
 - m) Train all relevant staff on the Mifepristone REMS Program requirements.

- n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.
- b. Mifepristone Sponsors must:
 - i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.
 - ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.
 - i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
 - *Pharmacy Agreement Form for GenBioPro, Inc.*
3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.
 - a. The patient must sign a *Patient Agreement Form* indicating that the patient has:
 - i. Received, read and been provided a copy of the *Patient Agreement Form*.
 - ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:
 - a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.
 - i. The distributors must put processes and procedures in place to:
 - 1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.
 - 2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.
 - 3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.
 - 4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.
 - 5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.
 - ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

- iii. Train all relevant staff on the Mifepristone REMS Program requirements.
 - iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.
- b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.
2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.
 3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.
 4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.
 5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.
 6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.
 7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg**PRESCRIBER AGREEMENT FORM**

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies:**
 - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
 - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
 - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

App. 000077

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
 - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
 - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
 - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

App. 000078

PRESCRIBER AGREEMENT FORM

Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies:**
 - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
 - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
 - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.



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 1-855-MIFE-INFO (1-855-643-3463) - www.MifeInfo.com

App. 000079

- If mifepristone will be dispensed through a certified pharmacy:
 - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
 - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
 - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to RxAgreements@GenBioPro.com or fax to 1-877-239-8036

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PATIENT AGREEMENT FORM

Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
 - a. I will take mifepristone on Day 1.
 - b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
 - heavy bleeding
 - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
 - a fever of 100.4°F or higher that lasts for more than four hours
 - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
 - severe stomach area (abdominal) pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
— these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

Provider Signature: _____ **Provider Name (print):** _____ **Date:** _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

App. 000081

MIFEPREX®(Mifepristone) Tablets, 200mg
PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
 - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
 - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
 - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
 - Track and verify receipt of each shipment of Mifeprex.
 - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
 - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
 - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
 - Train all relevant staff on the Mifepristone REMS Program requirements.
 - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____



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P.O. Box 4816-New York, NY 10185

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App. 000082

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred ___ email ___ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.



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PHARMACY AGREEMENT FORM**Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
 - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
 - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
 - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
 - Track and verify receipt of each shipment of mifepristone.
 - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
 - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
 - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
 - Train all relevant staff on the Mifepristone REMS Program requirements.
 - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred ___ email ___ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to RxAgreements@GenBioPro.com or fax to **1-877-239-8036**.



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s025

SUMMARY REVIEW

(b) (6) and (b) (6)
 (b) (6)
 (b) (6)
 Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
(b) (6) #	2022-1169
Reviewer Names	(b) (6) (b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.^a The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form, and Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

^a The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement” for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency’s REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

Per the Agency’s December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)^b to ensure that the benefits of the drug outweighed

^b NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.^c Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.¹⁻⁵ On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.⁶⁻⁷ The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
- b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
- c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form*, and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.⁸

^c Mifepristone is also approved in approximately 80 other countries.
https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.⁹
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.¹⁰
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system^d REMS could be implemented using the existing email and facsimile based system, (b) (4), as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4), as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4).
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

^d "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form*, *Pharmacy Agreement Form*, *Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form*, *Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6); hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.¹¹

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.¹¹ After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the “in-person dispensing requirement”), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient’s medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber’s signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.^e Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of

^e See e.g., 2020 Violence and Disruption Statistics, National Abortion Federation (Dec. 16, 2021), <https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/>; Amanda Musa, CNN, Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire, CNN WIRE (June 10, 2022), <https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/>.

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax.

(b) (4)

The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,¹³ while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

Reviewer's Comment: *We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

Reviewer's Comment: *We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
 - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.
- b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
 - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.
- c. Informing patients about the risk of serious complications associated with mifepristone.
 - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
 - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
 - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
 - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
 - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment: *We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4).

. The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form*. Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.^{13, 14}

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended. Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.
2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.
3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.
4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.
5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.
6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.
7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.
8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2022; 107:36-41. <https://doi.org/10.1016/j.contraception.2021.09.008>. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Initial Shared System REMS approval: 04/2019

Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg

Progestin Antagonist

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG**

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
 - a. To become specially certified to prescribe mifepristone, healthcare providers must:
 - i. Review the Prescribing Information for mifepristone.
 - ii. Complete a *Prescriber Agreement Form*. By signing¹ a *Prescriber Agreement Form*, prescribers agree that:
 - 1) They have the following qualifications:
 - a) Ability to assess the duration of pregnancy accurately
 - b) Ability to diagnose ectopic pregnancies
 - c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
 - 2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
 - b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
 - i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
 - ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form*.

¹ In this REMS, the terms “sign” and “signature” include electronic signatures.

- iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
 - iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
 - v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.
 - vi. If mifepristone will be dispensed by a certified pharmacy:
 - 1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.
 - 2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
 - 3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.
 - vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:
 - 1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.
 - 2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.
 - 3) Ensure that healthcare providers under their supervision follow guidelines i.-v.
 - c. Mifepristone Sponsors must:
 - i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.
 - ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:
 - 1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.
 - 2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.
 - iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.
 - iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.
 - v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.
- The following materials are part of the Mifepristone REMS Program:
- *Prescriber Agreement Form for Danco Laboratories, LLC*
 - *Prescriber Agreement Form for GenBioPro, Inc.*
 - *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
 - a. To become specially certified to dispense mifepristone, pharmacies must:
 - i. Be able to receive *Prescriber Agreement Forms* by email and fax.
 - ii. Be able to ship mifepristone using a shipping service that provides tracking information.
 - iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
 - iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
 - 1) Review the Prescribing Information for mifepristone.
 - 2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
 - a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
 - b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
 - c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
 - e) Track and verify receipt of each shipment of mifepristone.
 - f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
 - g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - i) Maintain records of *Prescriber Agreement Forms*.
 - j) Maintain records of dispensing and shipping.
 - k) Maintain records of all processes and procedures including compliance with those processes and procedures.
 - l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
 - m) Train all relevant staff on the Mifepristone REMS Program requirements.

- n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.
- b. Mifepristone Sponsors must:
 - i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.
 - ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.
 - i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
 - *Pharmacy Agreement Form for GenBioPro, Inc.*
3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.
 - a. The patient must sign a *Patient Agreement Form* indicating that the patient has:
 - i. Received, read and been provided a copy of the *Patient Agreement Form*.
 - ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:
 - a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.
 - i. The distributors must put processes and procedures in place to:
 - 1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.
 - 2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.
 - 3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.
 - 4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.
 - 5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.
 - ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

- iii. Train all relevant staff on the Mifepristone REMS Program requirements.
 - iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.
- b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.
- 2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.
- 3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.
- 4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.
- 5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.
- 6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.
- 7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg**PRESCRIBER AGREEMENT FORM**

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies:**
 - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
 - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
 - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

App. 000113

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
 - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
 - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
 - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

App. 000114

PRESCRIBER AGREEMENT FORM

Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies:**
 - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
 - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
 - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103
1-855-MIFE-INFO (1-855-643-3463) - www.MifeInfo.com

App. 000115

- If mifepristone will be dispensed through a certified pharmacy:
 - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
 - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
 - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to RxAgreements@GenBioPro.com or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103
1-855-MIFE-INFO (1-855-643-3463) - www.MifeInfo.com

App. 000116

PATIENT AGREEMENT FORM

Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
 - a. I will take mifepristone on Day 1.
 - b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
 - heavy bleeding
 - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
 - a fever of 100.4°F or higher that lasts for more than four hours
 - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
 - severe stomach area (abdominal) pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
— these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

Provider Signature: _____ **Provider Name (print):** _____ **Date:** _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

App. 000117

MIFEPREX®(Mifepristone) Tablets, 200mg
PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
 - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
 - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
 - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
 - Track and verify receipt of each shipment of Mifeprex.
 - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
 - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
 - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
 - Train all relevant staff on the Mifepristone REMS Program requirements.
 - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____



*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

App. 000118

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.



*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com
App. 000119

PHARMACY AGREEMENT FORM**Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
 - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
 - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
 - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
 - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
 - Track and verify receipt of each shipment of mifepristone.
 - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
 - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
 - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
 - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
 - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
 - Train all relevant staff on the Mifepristone REMS Program requirements.
 - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to RxAgreements@GenBioPro.com or fax to 1-877-239-8036.



The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics

a. Prescribers

- i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
- ii. Number and percentage of newly certified prescribers
- iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

b. Pharmacies

- i. Number of certified pharmacies
- ii. Number and percentage of newly certified pharmacies
- iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors

- i. Number of authorized wholesalers/distributors
- ii. Number and percentage of newly authorized wholesalers/distributors
- iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data

- a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
- b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data

- a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
 - i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
 - ii. The number of audits expected, and the number of audits performed
 - iii. The number and type of deficiencies noted
 - iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
 - v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

- vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)
- b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
 - i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
 - ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
 - 1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
 - 2. The source of the non-compliance data (e.g., self-reported, audit, other)
 - 3. A root cause analysis of the non-compliance
 - 4. Actions to prevent future occurrences and outcomes of such actions
 - iii. Prescriber compliance
 - 1. Number and percentage of certified prescribers who became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 - 2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
 - iv. Pharmacy compliance
 - 1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
 - 2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
 - 3. Number and percentage of pharmacies that became decertified as a result of non-compliance
 - Provide a summary of reasons for decertification (provide for the current reporting period)
 - 4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
 - 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
 - v. Wholesaler/distributor compliance
 - 1. Number of healthcare providers who successfully ordered mifepristone who were not certified
 - 2. Number of non-certified pharmacies that successfully ordered mifepristone
 - 3. Number of shipments sent to non-certified prescriber receiving locations
 - 4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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App. 000124

Center for Drug Evaluation and Research (CDER)

Application Type

NDA and ANDA

Application Number

020687 and 91178

Reviewer Names

(b) (6), (b) (6)

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Review Completion Date

December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the (b) (6), (b) (6) and (b) (6) (b) (6) rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the “in-person dispensing requirement” for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).^a This review provides the analysis of the

(b) (6) (b) (6) and the (b) (6) (b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

^a Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)^b to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
- b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
- c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form*, and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

^b NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.
- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.
- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.
- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.^c
- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.
- 1/12/2021: US Supreme Court granted a stay of that injunction.
- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

^c See Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*. FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.
- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.
- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.
- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.
- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.^d

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- [REDACTED] (b) (4)
[REDACTED]
- 11/02/2021: A [REDACTED] (b) (6) [REDACTED] (b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The [REDACTED] (b) (6) [REDACTED] (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

^d Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.
- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.
- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.
- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.
- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.
- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)
- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.
- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.
- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.
- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,^e and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

^e American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin Number 191, February 2018. Tubal Ectopic Pregnancy. <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy>. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.^f

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6), (b) (6), along with the (b) (6), (b) (6), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 (b) (6) review^g is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

^f REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>, Accessed November 15, 2021.

^g (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af803dc7bd&_afRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.^{h,i}

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies^{1,2} (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong³, Kerestes⁴). Aiken⁵ reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca⁶ described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

^h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.

ⁱ (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe⁷) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent “witnessed by the counselor”. Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient’s informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation’s 2020 Clinical Policy Guidelines for Abortion Care⁸ continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG⁹ and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017¹⁰ of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman¹¹ conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/gynecologists by Daniel in 2021¹² evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% –112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% –207%) and the South (+ 118%, 95% CI: 103% –134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)^j REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.¹³ The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

^j This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the ACOG case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.^{k,l}

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.^{m,n} (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of 12 of the 13

^k FDA General Advice Letter for NDA 20687, April 12, 2021.

^l FDA General Advice Letter for ANDA 091178, April 12, 2021.

^m NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.

ⁿ NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. (b) (4) non-certified healthcare provider dispensed one tablet to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed (b) (4) shipments representing (b) (4) tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The (b) (6) (b) (6) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.^{o,p}

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

^c (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

^p (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6).

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested^q to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

^q On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).^r

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

^r The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.^s

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman², Wiebe⁷, Rocca⁶) and dispensing mifepristone from pharmacies by mail (Grossman¹, Upadhyay¹⁴, Hyland¹⁵). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond¹⁶, Chong³, Anger¹⁷], Kerestes⁴, Aiken⁵ (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright¹⁸). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken¹⁹ (2017), Norton²⁰, Endler²¹). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman² conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

^s The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca⁶ conducted an observational study evaluating 605 participants at ≤ 63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion ($>97\%$) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,⁷ in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; $\geq 95\%$ calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman²), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe⁷) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service^t which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca⁶ study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman¹ published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

^t As noted in Mark²³ and Martin²⁴, most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay¹⁴ reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland¹⁵ describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have “full follow up”. The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman¹ study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland¹⁵ study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay¹⁴ study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.^{3,4,5,16, 17} Gynuity Health Projects conducted a prospective cohort study (the “TelAbortion” study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond¹⁶ from May 2016 to December 2018, Chong³ from May 2016 to September 2020 and Anger¹⁷ from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,⁴ reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken⁵ (2021).

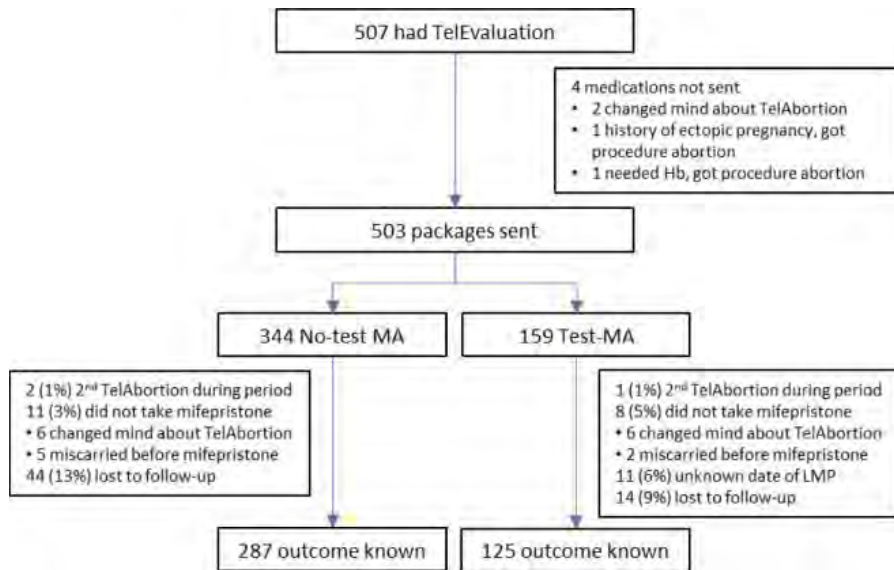
Raymond¹⁶ (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond¹⁶ (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.¹⁶ All participants received medications within 8 days.

Chong³ updated the findings from the Gynuity study described in Raymond¹⁶ and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger¹⁷ compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"^u based on a sample protocol published by Raymond²² (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

^u "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.²²



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes⁴ was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports^{3,16,17} and Kerestes⁴ support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond¹⁶, Chong³) and Kerestes⁴ report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken⁵ (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion^u (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken⁵ (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),^{3,16,17} Kerestes⁴, and Aiken⁵ (2021) support that efficacy of medical abortion was maintained. The Aiken⁵ study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond¹⁶ Chong³, and Kerestes⁴ all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's¹⁷ comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond¹⁶ publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond¹⁶ reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright¹⁸ reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken⁵ (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through “a partner organization” by mail.^v Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken¹⁹ (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort’s GA (almost 80% less than 7 weeks, labeled success for medical abortion \leq 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants’ self-reporting.

^v In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler²¹ and Norten²⁰ have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler²¹ compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the “first or second day of abortion” that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten²⁰ describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken¹⁹ (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.^w

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

^w The *Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications^x that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by “partner organizations”. The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

^x The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond¹⁶, Chong³, Anger¹⁷ and Kerestes⁴), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond¹⁶), may be associated with participants being located significant distances from their providers. The Aiken⁵ (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman¹ and Hyland¹⁵, where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's¹ interim analysis found no increases in SAEs. Hyland¹⁵ reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.^{j,y,z} Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.

z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.^{aa}

The above recommendations were discussed with the (b) (6) (b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (6) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (6) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

^{aa} Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

¹ Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2021; In press.
doi:<https://doi.org/10.1016/j.contraception.2021.09.008>

² Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstet Gynecol* 2021;137:613–22.

³ Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. *Contraception* 2021;104:43-48.

⁴ Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 Jul;104(1):49-53.
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⁵ Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. *BJOG* 2021;128:1464–1474.

⁶ Rocca CH, Puri M, et al. Effectiveness and safety of early medication abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. *PLoS ONE* 2018 13(1): e0191174. <https://doi.org/10.1371/journal.pone.0191174>

⁷ Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. *Contracept X*. 2020; 2: 100023.

⁸ National Abortion Federation 2020 Clinical Policy Guidelines for Abortion Care, available at https://5aa1b2xfmfh2e2mk03kk8rsx-wpengine.netdna-ssl.com/wp-content/uploads/2020_CPGs.pdf

⁹ American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology and the Society of Family Planning. Simultaneously published as ACOG Bulletin

Number 225: Medication abortion up to 70 days of gestation. *Obstet Gynecol* 2020;136(4): e31-e47 and in *Contraception* 2020; 102:225-236.

¹⁰ Jones HE, O'Connell White K, Norman WV, Guilbert E, Lichtenberg ES, Paul M. First trimester medication abortion practice in the United States and Canada. *PLoS ONE* 2017; 12(10): e0186487. <https://doi.org/10.1371/journal.pone.0186487>

¹¹ Grossman D, Grindlay K, Altshuler AL, Schulkin J. Induced abortion provision among a national sample of obstetrician-gynecologists. *Obstet Gynecol* 2019;133:477-483.

¹² Daniel S, Schulkin J, Grossman D. Obstetrician-gynecologist willingness to provide medication abortion with removal of the in-person dispensing requirement for mifepristone. *Contraception*. 2021;104:73-76

¹³ (b) (6) Review of the one-year REMS assessment report for the Mifepristone REMS Program, December 16, 2021.

¹⁴ Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. *JAMA Network Open*. 2021;4(8):e2122320. doi:10.1001/jamanetworkopen.2021.22320

¹⁵ Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. *Aust N Z J Obstet Gynaecol* 2018;58: 335-340.

¹⁶ Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception* 2019;100:173-177

¹⁷ Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. *Contraception* 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online.

¹⁸ Reynolds-Wright JJ, Johnstone A, McCabe K, et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmjsexrh-2020-200976

¹⁹ Aiken AR, Digon I, Trussell J, et al. Self reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. *BMJ* 2017;357:j2011.

²⁰ Norton H, Ilozumba O, Wilkinson J, et.al. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. *BJOG* 2021; <https://doi.org/10.1111/1471-0528.16765>.

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²³ Mark A, Foster A, Perritt J. The future of abortion is now: Mifepristone by mail and in-clinic abortion access in the United States. *Contraception* 2021;104:38-42

²⁴ Martin D, Miller A, Quesnel-Vallee, A, et al. Canada's global leadership on health 1. Canada's universal health care system: achieving its potential. *Lancet* 2018; 391:1718-35

7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from <i>Chelius v. Becerra</i> Plaintiffs (September 29, 2021)	
References included in the REMS review	
Aiken A et al. BJOG 2021; 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	Rationale for Exclusion
Am. Coll. of Obstetricians & Gynecologists, <i>Position Statement: Improving Access to Mifepristone for Reproductive Health Indications</i> (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., <i>Memorial Resolutions Adopted Unanimously No. 504 (2018)</i> https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, <i>Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone</i> (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
<p>Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625</p> <p>Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96</p> <p>Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235</p> <p>Barr-Walker J, et al PLoS One 2019;14(4): e0209991</p> <p>Grossman et al JAMA Network 2017;317(4):437, 437-438</p> <p>Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244</p> <p>Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262</p> <p>Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232</p> <p>Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689</p>	Focused on the logistics of accessing abortion care.
<p>CDC MMWR Abortion Surveillance – United States, 2018</p> <p>https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5 down</p>	Contains primarily general statistics on abortion care by state.

References cited in appendix from <i>Chelius v. Becerra</i> Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
References included in the REMS review
Grossman D. Obstet Gynecol 2019;133 (3): 477-483

Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
Winikoff B et al. Obstet Gynecol 2012; 120: 1070-1076 reviewed in 2016 clinical memo	
Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	Rationale for Exclusion
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012; 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

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App. 000174

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s025

OTHER REVIEW(S)

Review of Labeling

(b) (6)

NDA Number/Supplement	020687/025
Applicant	Danco Laboratories, LLC
Product Name	Mifeprex (mifepristone) tablets
Therapeutic Class	Progestin antagonist
Indication	For the medical termination of intrauterine pregnancy through 70 days gestation, in a regimen with misoprostol
Material Reviewed	Prescribing Information and Medication Guide received December 16, 2022
Date of Review	January 3, 2023
Reviewer	(b) (6)

This memorandum is the (b) (6) (Division's) review of the proposed revisions to the labeling and Medication Guide for Mifeprex submitted by Danco Laboratories (Applicant) on December 16, 2022. These revisions are to align the language in the Prescribing Information and the Medication Guide with the proposed modification to the Mifepristone single, shared system Risk Evaluation and Mitigation Strategy (REMS) (referred to as the Mifepristone REMS Program) submitted under NDA 020687/Supplement-025, as amended.

1. Background

Mifeprex (mifepristone), in a regimen with misoprostol, is indicated for the medical termination of intrauterine pregnancy through 70 days gestation. Mifeprex and its approved generic are subject to the Mifepristone REMS Program to mitigate the risk of serious complications associated with mifepristone. The Mifepristone REMS Program consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (ETASU A).
- Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of certified prescribers (ETASU C).
- Informing patients about the risk of serious complications associated with mifepristone (ETASU D).

On December 16, 2021, FDA sent REMS Modification Notification letters to the Applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg (Danco

Laboratories and GenBioPro, respectively). The letters informed the Applicants of the FDA's determination that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks by: (1) removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") (ETASU C) and (2) to add the requirement for certification of pharmacies that dispense the drug (ETASU B).¹ For a detailed discussion of the modification recommendations refer to the REMS Modification Rationale Review, jointly completed by the (b) (6) and the (b) (6) on December 16, 2021.²

As proposed by the Applicants in their December 16, 2022, amendments to their pending supplements, the modified goal of the Mifepristone REMS Program would read as follows:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

The Division reviewed the Applicant's proposed revisions to the approved Mifeprex labeling under NDA 020687 Supplement 025, as amended, which provides REMS document and materials to align with the changes described in the REMS Modification Notification letters. Specifically, the requirement that mifepristone must be dispensed to patients in certain healthcare settings (ETASU C) was removed and the dispensing of mifepristone through specially certified pharmacies (ETASU B) was added. This REMS modification ensures that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. There were no changes to ETASU A and ETASU D (prescribers must be specially certified and mifepristone must be dispensed to patients with evidence of safe use conditions, respectively).

On December 16, 2022, final labeling for the Mifeprex Prescribing Information (PI) and Medication Guide (MG) were received to align with the Mifepristone REMS Program modification. This submission is reviewed below. Review of the labeling changes made in the PI

¹ REMS Modification Notification letter dated December 16, 2021.

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80633e9f>

² REMS memorandum dated December 16, 2021.

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80633d74>

and in the MG for the approved generic (ANDA 091178) will be completed by the (b) (6)

2. Review of Labeling Changes

Prescribing Information and Medication Guide

The following two changes were made in both the PI and MG for Mifeprex:

1. Gender neutral edits were made throughout the PI and MG.

Reviewer comment: The Division agrees to the use of gender-neutral language to align with such changes previously approved for documents associated with this REMS.

2. Removal of instructions for patients to take the MG when they visit an emergency room or another healthcare provider who did not prescribe Mifeprex, so the provider knows that the patient is undergoing a medical abortion.

Reviewer comment: The Applicant requested this change. Removal of the instructions in the PI and MG aligns with the updated Patient Agreement Form submitted in Supplement S-025, which removes instructions for patients to take the MG to healthcare visits with providers who did not provide Mifeprex. Although these instructions were added to the MG a number of years ago, upon further consideration the Division agrees with removing them because patients seeking emergency medical care are not likely to carry a MG with them, the MG is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

Prescribing Information

Additional changes were made in the PI to include pharmacy dispensing in Section 5.3 Mifepristone REMS Program and Section 17 Patient Counseling Information. Typographical errors were corrected in Sections 16 and 17.

1. Section 5.3 Mifepristone REMS Program

The Applicant proposed changes to one of the three bulleted ETASU requirements, to state “MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.”

Reviewer comment: The revised language is consistent with the REMS modification to include certified pharmacy dispensing. The Division agrees with the proposed language.

2. Section 17 Patient Counseling Information

The Applicant proposed changes to one of the two bulleted ETASU requirements, to state “MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.”

Reviewer comment: As above, the revised language for the PI for the approved MIFEPREX product is consistent with the REMS modification to include certified pharmacies and the Division agrees with the proposed language.

3. Section 16 How Supplied/Storage and Handling and Section 17 Patient Counseling Information

- a. Both Sections 16 and 17 refer to the “mifepristone REMS Program” which was edited to “Mifepristone REMS Program”.
- b. In Section 17, reinstatement was made of “a” before Patient Agreement Form in the bullet “Patients must sign a Patient Agreement Form”.

Reviewer comment: The Applicant will be informed of these minor edits.

Medication Guide

Additional changes were made in the MG within the section titled “How should I take Mifeprex?”, as follows:

1. Addition of obtaining Mifeprex at a pharmacy: “Mifeprex will be given to you by a healthcare provider or pharmacy.”
2. Removal of statement “Your healthcare provider will either give you or prescribe for you 4 misoprostol tablets to take 24 to 48 hours later.”

Reviewer comment: The proposed MG changes for Mifeprex are acceptable to (b) (6). The addition of Mifeprex to be dispensed at a pharmacy reflects the REMS modification change. The statement on misoprostol dispensing is removed because it is not necessary to specify in the Mifeprex labeling how misoprostol is dispensed. The directions to take misoprostol tablets 24 to 48 hours after taking mifepristone are maintained in the Mifeprex patient instructions.

3. Conclusion

We received the final proposed labeling revisions to the Prescribing Information and Medication Guide from the Applicant on December 16, 2022. The Prescribing Information and Medication Guide for Mifeprex were revised to align with the Mifepristone REMS Program modification, which include removing the requirement that Mifeprex be dispensed only in certain healthcare settings and adding the requirement for pharmacy certification. The proposed labeling revisions were reviewed and found to be acceptable with minor edits.

All labeling changes outlined above will be applied to the approved generic mifepristone (ANDA 091178). The (b) (6) will review labeling for the approved generic and ensure it mirrors the updated approved labeling for the Mifeprex product.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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DATE: December 23, 2022

SUBJECT: Review of Supplemental Drug Applications Proposing Modifications to the
Mifepristone REMS Program

FDA is currently reviewing a supplemental new drug application from Danco Laboratories, LLC (Danco) and a supplemental abbreviated new drug application from GenBioPro, Inc. (GBP) that propose to modify the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program as approved under Danco's new drug application for Mifeprex (mifepristone) (NDA 020867) and GBP's abbreviated new drug application for Mifepristone Tablets 200 mg (ANDA 091178). Citing the Comstock Act, 18 U.S.C. §§ 1461, 1462, Plaintiffs in *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*, No. 2:22-cv-00223-Z (N.D. Tex.), have alleged that FDA's actions regarding mifepristone do not comply with "federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other common carrier of any substance or drug intended for producing abortion" and also that FDA "failed to acknowledge and address" those laws. Complaint ¶¶ 22, 392 (Nov. 18, 2022). This memorandum notes that the Office of Legal Counsel of the United States Department of Justice, which provides controlling advice to Executive Branch officials on questions of law, has concluded that the Comstock Act provisions cited by Plaintiffs "[do] not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates [these provisions]." Memorandum for Thomas J. Marshall, General Counsel, United States Postal Service, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions*, at 15 (December 23, 2022).¹ Thus, even if the Comstock Act provisions bear on FDA's analysis of the pending supplemental drug applications, in light of the conclusions set forth by the Office of Legal Counsel, they pose no issue for FDA's approval of the applications.

¹ The Office of Legal Counsel's analysis applies to 18 U.S.C. § 1461 and § 1462. *See id.* at 1 n.3.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s025

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification: Removal of a Requirement and Addition of a Requirement
U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

(b) (6)

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NDA/ANDA #s: NDA 20687, ANDA 91178
Products: Mifeprex, mifepristone, 200 mg tablets
APPLICANTS: Danco, GenBioPro
FROM: (b) (6)
 (b) (6)
DATE: December 16, 2021

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifeprex was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H) and subsequently was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007. The Mifeprex REMS with elements to assure safe use (ETASU) was approved on June 8, 2011 and a supplemental efficacy application and REMS modification was approved on March 29, 2016. The Mifepristone REMS Program (a single, shared system REMS that currently includes NDA 020687 and ANDA 91178) was approved on April 11, 2019.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone. The current Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use include requirements for prescriber certification (ETASU A), that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient, indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone.

The requirement under ETASU C that mifepristone be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals, is referred to as the “in-person dispensing requirement.”

On January 31, 2020 the Secretary of Health and Human Services (HHS) declared COVID-19 a public health emergency (PHE) as of January 27, 2020. During the COVID-19 pandemic, there have been periods when the in-person dispensing requirement has not been enforced. From July

13, 2020 until January 12, 2021, enforcement was barred by an injunction issued in the *ACOG v. FDA* litigation. More recently, on April 12, 2021, the Agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 PHE, which is still ongoing as of the date of this review. These circumstances have provided additional information regarding the in-person dispensing requirement as there have been periods when the in-person dispensing requirement was not enforced.

As part of the May 7, 2021, joint motion to stay the *Chelius v. Becerra* litigation, the Agency agreed to undertake a full review the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).¹

After consultations between the (b) (6), analyzing several different sources of information, including published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius* litigation, we determined that the approved REMS for mifepristone could be modified without adversely impacting patient safety. Importantly, our review did not identify any differences in adverse events between periods when the in-person dispensing requirement was being enforced and periods when that requirement was not being enforced. The data suggested that the requirements for prescriber certification (ETASU A) and the Patient Agreement Form (ETASU D) should be maintained, while the in-person dispensing requirement (under ETASU C) could be removed, to reduce the burden imposed by the REMS. In determining that the in-person dispensing requirement could be removed, we concluded that a new requirement for pharmacy certification (ETASU B) is necessary to ensure the benefits of the product outweigh the risks.

(b) (6) and (b) (6) assessment and recommendations were (b) (6) (b) (6) on November 2, 2021. The (b) (6) unanimously agreed with our recommendations.

For more detailed information on the review and assessments of the information, refer to the REMS Modification Rationale Review, jointly completed by (b) (6) and (b) (6) on December 16, 2021.

In conclusion, provided all other conditions of the Mifepristone REMS Program are met and that the other elements of the REMS are maintained (ETASU A and D), the following are required:

1. Modification of the Mifepristone REMS Program to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals. This would allow, for example, dispensing of mifepristone by mail, via certified prescribers or pharmacies, in addition to in-person

¹ Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C .

We find that this provision is no longer necessary to ensure that the benefits of the drug outweigh the risks and that removing it will help minimize the burden of complying with the REMS on the healthcare delivery system.

2. Modification of the Mifepristone REMS Program to add a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

Based on the (b) (6) and (b) (6) determination that a modified REMS with the components described above is necessary to reduce the burden imposed by the REMS and ensure the benefits of mifepristone outweigh the risks, FDA is requiring submission of the proposed REMS modification within 120 days of the date of the notification letter.

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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022, and December 9, 2022 (sequences 25 and 93 respectively)
Targeted Action Date	December 19, 2022
(b) (6) #	2022-1169
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Review Completion Date	December 14, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to REMS Modification Notification letters issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

The comments in this review focus on the Applicants’ amendments that were received on December 9, 2022, which included updates to the REMS Document and materials that were discussed and edited during a teleconference between the Agency and Applicants on December 8, 2022.

2. Comments to the Sponsor

General Comments

The documents have been revised for you per the comments below.

REMS Document

We have revisions in the REMS document in the following sections:

II. A.2.a.iv.2) I, the language must be updated to replace “provider” with “prescriber,” and to remove the phrase that (b) (4)

(b) (4)

II.A.2.c.ii A requirement was added to ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form* (b) (4)

(b) (4)

II. A.3, we have the following edits to align with the statute. Mifepristone must be (b) (4) dispensed (b) (4) to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

II.B.5 must be updated to include: Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

REMS Supporting Document

We require clarification and revisions in several sections. A red-lined Supporting Document has been attached for reference.

The wording in the Supporting Document was not consistent with the REMS document and REMS materials. Throughout the Supporting Document, the document was revised to align with the wording in the REMS Document, *Prescriber Agreement Form*, *Patient Agreement Form*, and *Pharmacy Agreement Form*.

The Supporting Document is inconsistent with respect to grammar and punctuation, as well as with respect to capitalization, italicization, and terminology. Review and revise the Supporting Document for grammar and punctuation, and for consistency in capitalization, italicization, and terminology.

The term “(b) (4)” was replaced with “supervised healthcare providers” where applicable.

There was minimal information about account set up processes for the certified prescribers and pharmacies. Include explanation of how accounts will be set up and maintained and what information from the account set up process will be used for REMS assessments.

There was also minimal information about how Sponsors will communicate with each other when stakeholders report information that the other needs to know such as when stakeholders report patient deaths to the wrong Sponsor or when decertifications of pharmacies or prescribers take place. Clarify what actions require timely communication between Sponsors and the timeline in which these actions should be reported to the other Sponsor.

Prescriber Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

(b) (4). This data will be available through the account set up process.

Pharmacy Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

(b) (4) must be removed as it is redundant to the language later in the form. The confidentiality requirement later in the form, under the requirements that certified pharmacies must put processes and procedures in place to accomplish, must be further aligned with the confidentiality requirement added to the REMS Document (discussed above).

Patient Agreement Form

The Patient Agreement Form is acceptable.

Resubmission Instructions

Accept all track changes and submit the following revised REMS materials by 12/16/22. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents and one clean compiled PDF file that includes the REMS Document and all REMS materials in their final format:

- REMS Document
- Prescriber Agreement Form for Danco Laboratories, LLC
- Prescriber Agreement Form for GenBioPro, Inc.
- Pharmacy Agreement Form for Danco Laboratories, LLC
- Pharmacy Agreement Form for GenBioPro, Inc.
- Patient Agreement Form
- REMS Supporting Document with the Assessment Plan

Appendix

- REMS Document
- Prescriber Agreement Form for Danco Laboratories, LLC
- Prescriber Agreement Form for GenBioPro, Inc.

Pharmacy Agreement Form for Danco Laboratories, LLC
Pharmacy Agreement Form for GenBioPro, Inc
REMS Supporting Document

30 Pages of Draft REMS Documents Have Been Withheld in Full as B4 (CCI/TS)
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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022
(b) (6) #	2022-1169
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Review Completion Date	December 8, 2022
Subject	Review of Proposed Major REMS Modification: Draft REMS Assessment Plan Comments
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and from GenBioPro Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to a REMS Modification Notification letter issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

The comments in this review focus on revisions to the REMS Assessment Plan.

2. Comments to the Applicant

We have provided a draft REMS Assessment Plan as discussed on the December 7, 2022 teleconference. The proposed Agency edits have been marked in tracked changes from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval Letter. Refer to the attached Draft REMS Assessment Plan with tracked changes. Review of the REMS proposal is ongoing; these comments should not be considered final.

We have the following comments:

1. Provide each assessment plan metric for the two previous, current, and cumulative reporting periods (if applicable) for both the NDA and ANDA unless otherwise noted.
2. The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.
3. A REMS Certification Statistics metric was added to capture the following:
 - a. Total number of certified, newly certified, and active prescribers along with a summary of the practice setting of the certified prescribers and the method in which they became certified.
 - b. Total number of certified, newly certified, and active certified pharmacies.
 - c. Total number of authorized, newly authorized, and active wholesaler/distributors.
4. A Utilization Data metric was added to capture wholesaler/distributor shipment and pharmacy data.
5. A REMS Compliance Data metric was added to capture stakeholder audit results and a summary of instances of non-compliance and actions taken to address non-compliance.

Resubmission Instructions

Submit the revised REMS Assessment Plan in the REMS Supporting Document with your 12/9/22 submission. Accept the tracked changes in the draft REMS Assessment Plan with which you agree and only indicate any new changes you propose as tracked changes in your next submission. The submission should include clean Word, tracked changes Word, and pdf formatted versions of the following document.

Appendix

REMS Assessment Plan

4 Pages of Draft REMS Documents Have Been Withheld in Full as B4 (CCI/TS)
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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022
PDUFA Date	December 19, 2022
(b) (6) #	2022-1169
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
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Review Completion Date	December 5, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to REMS Modification Notification letters issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

The comments in this review focus on the Applicants’ amendments that were received on October 19 and 20, 2022 and November 30, 2022 (REMS Document). The comments also reflect the REMS Document that was further discussed and edited during a teleconference between the Agency and Applicants on December 1, 2022.

2. Comments to the Sponsor

General Comments

We have updated the REMS Document as discussed during the December 1, 2022 teleconference and aligned the REMS materials. Your edits, where the Agency agrees, have been accepted and Agency edits have been marked in tracked changes. Refer to the attached, red-lined REMS Document and REMS Materials. Review of the REMS proposal is ongoing; these comments should not be considered final.

- The Agency has determined that further clarification that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program is appropriate in the *Prescriber Agreement Form* and has been added. This clarification provides flexibility for certified prescribers in overseeing REMS implementation and compliance. The certified prescriber may do so in a manner that may include the use of a larger healthcare team and delegation of tasks. We have determined that to make additional changes to the prescriber certification requirements would constitute a substantive modification to the REMS that would go beyond the required REMS modifications set forth in the December 16, 2021 REMS Modification Notification letters. Adequate rationale is required to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act. Your application does not include such adequate rationale.
- We agree that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone is dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification and have added this clarification to the *Prescriber Agreement Forms* and *Pharmacy Agreement Forms*. These clarifications negate the need for further clarification in the REMS Document as you proposed in the footnote to section II.A.2.
- Moving forward, italicize all proper names of forms e.g. *Prescriber Agreement Form* in the REMS.

Prescriber Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

The instructions on the *Prescriber Agreement Forms* were revised for clarity. Prescriber information collected on the forms was updated to capture practice setting (b) (4) address, and an additional line for medical license state was added. Duplicative or unnecessary instructions have been removed.

Pharmacy Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

The titles of the *Pharmacy Agreement Forms* were edited to remove “(b) (4).” The REMS pharmacy requirements will dictate whether a pharmacy can participate in the Mifepristone REMS Program and therefore (b) (4). Additional information fields regarding authorized representatives and pharmacies were added and the term “(b) (4)” was replaced with “pharmacy.” Duplicative or unnecessary instructions have been removed.

Patient Agreement Form

The first paragraph of the form has been aligned with the currently approved Mifepristone REMS Program and clarification that signatures on the document can be written or electronic was added. Risk information regarding ectopic pregnancy has been reorganized. (b) (4)

Resubmission Instructions

Accept all track changes and submit the following revised REMS materials by 12/08/22. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents and one clean compiled PDF file that includes the REMS Document and all REMS materials in their final format:

- REMS Document
- Prescriber Agreement Form for Danco Laboratories, LLC
- Prescriber Agreement Form for GenBioPro, Inc.
- Pharmacy Agreement Form for Danco Laboratories, LLC
- Pharmacy Agreement Form for GenBioPro, Inc
- Patient Agreement Form
- REMS Supporting Document with the Assessment Plan
- Updated prescription label and Medication Guide

Appendix

- REMS Document
- Prescriber Agreement Form for Danco Laboratories, LLC
- Prescriber Agreement Form for GenBioPro, Inc.
- Pharmacy Agreement Form for Danco Laboratories, LLC
- Pharmacy Agreement Form for GenBioPro, Inc
- Patient Agreement Form

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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively)
Action Date	December 19, 2022
(b) (6) #	2022-1169
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
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Review Completion Date	November 23, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and from GenBioPro Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to a REMS Modification Notification letter issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

Danco amended their submission on October 19, 2022 and GBP amended their submission on October 20, 2022.

2. Comments to the Sponsor

General Comments

For clarity, we have used the approved REMS Document to provide edits. Your proposed edits and Agency edits have been marked in tracked changes. Refer to the attached, red-lined REMS Document. Review of the REMS proposal is ongoing; these comments should not be considered final.

We have additional questions that must be addressed. Refer to the red-lined REMS Document attached. You must address the following question with your next submission:

1. Refer to the distributor requirement on page five (in all markup), “Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of mifepristone” (underline added for emphasis)

Clarify whether the packages that are tracked by the distributors will still be done by serial numbers or if tracking will only use the NDC and lot numbers.

REMS Goal

(b) (4)

We have revised the goal to the following:

“The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers or by certified pharmacies.
- c) Informing patients about the risk of serious complications associated with mifepristone.”

REMS Document

We have provided edits to the REMS Document to reflect the requirements communicated in the December 16, 2021 letter and to incorporate additional requirements. We have determined that for this modification we will not be using the format for the REMS that is in the 2017 draft Guidance for Industry - Format and Content of a REMS Document, as not all requirements are easily transferred to the newer format and may result in creating unnecessary confusion to stakeholders. Note that all REMS Materials and the REMS Supporting Document must align with the REMS Document.

Prescriber requirements were edited for clarity, brevity and to align with certified prescriber qualifications in the currently approved REMS. Additional requirements were needed to address situations that may arise if a certified prescriber opts to dispense through a certified pharmacy.

Pharmacy requirements were revised: to ensure pharmacies are able to ship mifepristone using a shipping service that provides tracking information, to include the use of an authorized representative to coordinate REMS implementation on behalf of the pharmacy, to dispense mifepristone such that it is delivered to the patient within four calendar days of the date the pharmacy receives the prescription, and to confirm with the prescriber and document the appropriateness of dispensing mifepristone for patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription. Additional record-keeping and reporting requirements were also added.

Additional Sponsor requirements were added to support prescriber, pharmacy, and distributor REMS stakeholder requirements, and to ensure the REMS operates as intended.

REMS Supporting Document

The REMS Supporting Document must be included in your next submission and is necessary to help us understand how these changes will be implemented before we can take an action.

Resubmission Instructions

Submit the following revised REMS materials by 11/30/22. Accept the track changes in the REMS Document with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

- REMS Document
- REMS Supporting Document

Appendix

REMS Document

5 Pages of Draft REMS Documents Have Been Withheld in Full as B4 (CCI/TS)
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s025

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 020687

REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC

(b) (4), (b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6) :

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

App. 000207

complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments. The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687/S-000
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

If you have any questions, call (b) (6), at (b) (6).

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

12/16/2021 03:09:07 PM

App. 000211

EXHIBIT 4

Declaration of Dr. Donna Harrison

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION**

**ALLIANCE FOR HIPPOCRATIC
MEDICINE**, on behalf of itself, its members,
and their members, and their members'
patients; **AMERICAN ASSOCIATION OF
PRO-LIFE OBSTETRICIANS AND
GYNECOLOGISTS**, on behalf of itself, its
members, and their patients; **AMERICAN
COLLEGE OF PEDIATRICIANS**, on
behalf of itself, its members, and their
patients; **CHRISTIAN MEDICAL &
DENTAL ASSOCIATIONS**, on behalf of
itself, its members, and their patients;
SHAUN JESTER, D.O., on behalf of
himself and his patients; **REGINA FROST-
CLARK, M.D.**, on behalf of herself and her
patients; **TYLER JOHNSON, D.O.**, on
behalf of himself and his patients; and
GEORGE DELGADO, M.D., on behalf of
himself and his patients,
Plaintiffs,

v.

**U.S. FOOD AND DRUG
ADMINISTRATION; ROBERT M.
CALIFF, M.D.**, in his official capacity as
Commissioner of Food and Drugs, U.S. Food
and Drug Administration; **JANET
WOODCOCK, M.D.**, in her official capacity
as Principal Deputy Commissioner, U.S.
Food and Drug Administration **PATRIZIA
CAVAZZONI, M.D.**, in her official capacity
as Director, Center for Drug Evaluation and
Research, U.S. Food and Drug
Administration; **U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES**; and
XAVIER BECERRA, in his official capacity
as Secretary, U.S. Department of Health and
Human Services,
Defendants.

Case No. _____

DECLARATION OF DR. DONNA HARRISON

I, Donna Harrison, a citizen of the United States of America and a resident of Berrien Center, Michigan, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist.
3. I received my medical degree from the University of Michigan and completed my residency at a University of Michigan affiliate hospital, St. Joseph Mercy Hospital.
4. I am a diplomate of the American Board of Obstetrics and Gynecology.
5. I serve as the Chief Executive Officer of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG).
6. I also serve as the President of Plaintiff Alliance for Hippocratic Medicine (AHM).
7. I am familiar with AAPLOG, its members, their fields of practice, and AAPLOG's policies and positions, including as set forth in the complaint, which I have reviewed.
8. AAPLOG is the largest organization of pro-life obstetricians and gynecologists ("OB/Gyns") in the world and is headquartered in Indiana. AAPLOG includes OB/Gyns and other physicians, with more than 7,000 medical professionals nationwide and more than 300 members in Texas.

AAPLOG members oppose elective abortion and are committed to the care and well-being of their patients including both pregnant women and their unborn children. AAPLOG members are concerned about the adverse impacts of chemical abortion on their practice of medicine.

9. AAPLOG's mission includes advocating on behalf of its members, including in litigation.

10. AAPLOG sues in this case on behalf of itself and its members.

11. I am also familiar with AHM, its members, their members' fields of practice, and AHM's policies and positions, including as set forth in the complaint, which I have reviewed.

12. AHM is a nonprofit organization that upholds and promotes the fundamental principles of Hippocratic medicine. AHM is incorporated in the State of Texas and has its registered agent in Amarillo, Texas.

13. AHM's members include the membership of the American Association of Pro-Life Obstetricians and Gynecologists, American College of Pediatricians, Catholic Medical Association, Christian Medical and Dental Associations, and Coptic Medical Association of North America. In opposing chemical abortion, AHM's members are concerned about the safety and well-being of pregnant women and girls, their preborn children, and chemical abortion's adverse impacts on the practice of medicine.

14. AHM sues in this case on behalf of itself and its members.

15. I am familiar with chemical abortion drugs, their use, and the complications that accompany chemical abortion.

16. As part of my duties and responsibilities at AAPLOG, I have authored several studies on the approval of mifepristone as an abortifacient. Among these, I co-authored two studies with other physicians and scholars examining the adverse events associated with the use of mifepristone. Our studies of the real-world use of mifepristone concluded that significant morbidity and mortality have occurred following the use of mifepristone as an abortifacient. We recommended that a pre-abortion ultrasound should be required to rule out ectopic pregnancy and confirm the gestational age of the unborn child. We concluded that the FDA's adverse event reporting system is grossly inadequate to evaluate real-world complications and significantly underestimates adverse events from mifepristone. One major reason that the FAERS database does not reflect real world complications is that FDA only required the manufacturer to report complications, and the manufacturer in turn obtains data from the abortionists. However, as our studies of the FAERS database indicate, most complications are not handled by the abortion provider, but rather by the Emergency Department, and the Emergency Department physician has no knowledge of the reporting process or obligation to report those complications to the manufacturer or to the FDA. See Kathi Aultman, et al., *Deaths and Severe Adverse Events After the Use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 36

Issues L. Med. 3 (2021), <https://pubmed.ncbi.nlm.nih.gov/33939340/>;

Margaret M. Gary & Donna J. Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, 40 Ann. Pharmacother. 171 (2006), <https://pubmed.ncbi.nlm.nih.gov/16380436/>.

17. In addition, as part of my duties and responsibilities at AAPLOG, I co-authored a paper comparing the published complications after use of mifepristone from Planned Parenthood in 2009 and 2010 and compared those numbers to the complications in the FDA Adverse Event Reporting System for the same time period. We found that Cleland identified 1,530 Planned Parenthood mifepristone cases with specific adverse events (AEs) for 2009 and 2010. For this period, FAERS online dashboard includes a total (from all providers) of only 664, and the FDA released only 330 adverse event reports (AERs) through Freedom of Information Act (FOIA) requests. Cleland identified 1,158 ongoing pregnancies in 2009 and 2010. FAERS dashboard contains only 95, and only 39 were released via FOIA requests. We concluded that there are significant discrepancies in the total number of AERs and specific AEs for 2009 and 2010 mifepristone abortions reported in 1) Cleland's documentation of Planned Parenthood AEs, 2) FAERS dashboard, and 3) AERs provided through FOIA. These discrepancies render FAERS inadequate to evaluate the safety of mifepristone abortions. See Christina A Cirucci, et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting*

System and Those Obtained Through the Freedom of Information Act, 8 Health Servs. Rsch. & Managerial Epidemiol. 23333928211068919 (2021), <https://pubmed.ncbi.nlm.nih.gov/34993274/>.

18. I also co-authored a study looking at the real-world effects of the FDA Approval of Mifeprex on Emergency Room utilization after Mifeprex abortions. The massive increased utilization of Emergency Departments to manage abortion complications is a predictable consequence of the FDA's failure to require the same qualifications of Mifeprex abortion providers as were mirrored in the clinical trial for Mifeprex approval.
19. Because the FDA abandoned the post marketing requirement that abortion providers have admitting privileges to handle their own complications and allowed abortion providers who lack the ability to handle complications to dispense Mifeprex, the predictable consequence is the explosion of Mifeprex complications including hemorrhage, adding to the current shortage of blood and blood products across the United States. See James Studnicki, et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999-2015*, 8 Health Servs. Rsch. & Managerial Epidemiol. 23333928211053965 (2021), <https://pubmed.ncbi.nlm.nih.gov/34778493/>.
20. I am familiar with the FDA's regulation of chemical abortion drugs, including mifepristone and misoprostol. As part of my duties and responsibilities at AAPLOG, I co-authored the original 2002 Citizen Petition and the 2019

Citizen Petition filed by AAPLOG and others to challenge the FDA's actions on chemical abortion drugs. As part of my duties and responsibilities at AAPLOG, I also co-authored a study detailing the aberrancies of the FDA Approval process as it affects real-world patients. See Byron C. Calhoun & Donna J. Harrison, *Challenges to the FDA Approval of Mifepristone*, 38 Ann. Pharmacother. 163 (2004), <https://pubmed.ncbi.nlm.nih.gov/14742814/>.

21. In a chemical abortion, women take mifepristone to terminate the pregnancy by killing the preborn child. Women then take misoprostol to expel all pregnancy tissues, including the preborn child, through contractions and cramping.
22. Women who take chemical abortion drugs experience more complications than those who have surgical abortions.
23. There are many intense side effects for women who take chemical abortion drugs, including cramping and heavy bleeding.
24. Since the FDA's 2000 Approval of Mifeprex (the chemical abortion drug regimen consisting of mifepristone and misoprostol), medical professionals have needed to treat women and girls who have suffered from chemical abortion and experienced complications.
25. Mifepristone and misoprostol are serious drugs that should not be administered without medical supervision. The FDA's actions to eliminate the necessary supervision of these drugs harm women and obstetrics professionals, including AHM, AAPLOG, and their members.

26. Since the FDA's 2016 Major Changes to eliminate safeguards for the use of Mifeprex, AAPLOG members have needed to treat an increasing rate of women and girls who suffer complications from chemical abortion.
27. The increase in the frequency of complications harms medical providers—including AHM and AAPLOG members—because they end up managing the increase in complications.
28. When women suffer complications from chemical abortions, it can overwhelm the medical system and consume crucial limited medical resources, including blood for transfusions, physician time and attention, space in hospital and medical centers, and other equipment and medicines.
29. The increased occurrence of complications related to chemical abortions also multiplies the workload of healthcare providers, including AHM and AAPLOG members, in some cases by astronomical amounts. This is especially true in maternity care “deserts” (i.e., geographic areas where there are not a large number of OB/Gyn providers for patients).
30. For OB/Gyn professionals, the increase in complications due to increased use of chemical abortion drugs means that the typical care given to patients goes from simple patient management to complicated patient management. Patients who suffer complications from chemical abortions require significantly more time and attention from providers than the typical OB/Gyn patient requires.

31. In my experience, many patients do not fully understand the nature of chemical abortion or the risks that these drugs present to them. This results in an increase in the frequency of women seeking emergency medical care for side effects such as cramping, heavy bleeding, and severe pain even if they are not suffering an adverse event.

32. I understand that the FDA has removed the requirement for abortionists to report all adverse events for mifepristone.

33. Many doctors likely do not know about the need to report adverse events related to chemical abortion to the FDA. Similarly, many doctors likely do not know how to report adverse events. This means that complications handled by practitioners other than the abortionist are rarely reported to the FDA or the manufacturer.

34. I personally know of practitioners, including AAPLOG members, who have tried to report adverse events related to chemical abortion drugs to the FDA. The process is complicated, cumbersome, and time-consuming. The adverse event reporting requirements and the FAERS submission process harm medical practices by taking away significant time from a doctor to treat and meet with patients.

35. The FDA's decision not to require abortionists to report all adverse events for mifepristone harms women and girls because this deregulatory action creates an inaccurate and false safety profile for the use of mifepristone and misoprostol.

36. Without an accurate picture of the adverse effects of widespread chemical abortion drug use, physicians cannot effectively practice evidence-based medicine. If the FDA is not collecting the vast majority of adverse events to understand the true risk, healthcare providers cannot assess the risks of a particular course of treatment and inform their patients accordingly.
37. The inability of providers to adequately inform women of the known risks associated with chemical abortion drugs precludes women and girls from giving informed consent to taking these drugs. The lack of information also harms the patient-doctor relationship with all medical care providers because the patients no longer trust that their healthcare providers are telling the truth. This even harms organizations and practitioners who do not support or practice chemical abortion, including AHM, AAPLOG, and their members.
38. Due to inadequate adverse event reporting, the true rates of risks associated with chemical abortion drugs remain unknown and undercounted. This prevents AHM and AAPLOG from providing the public, their members, and their members' patients with accurate statistics and complete information regarding potential risks associated with the use of chemical abortion drugs.
39. The inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and complicates AHM's and AAPLOG's purpose to support women's health and to educate doctors, their patients, and the public about these dangers.

40. AHM and AAPLOG need to divert limited time, energy, and resources to compensate for this lack of information by conducting their own studies and analyses of the available data. This diversion of time, energy, and resources comes to the detriment of other advocacy and educational efforts of AHM and AAPLOG, including their efforts regarding the dangers of surgical abortion, the conscience rights of doctors, and the sanctity of life at all stages.

41. On behalf of AAPLOG and serving as the chairperson for AAPLOG's Subcommittee on Mifeprex, I submitted a Citizen Petition in 2002 challenging the FDA's approval of Mifeprex and requesting an audit of the Mifeprex clinical studies. AAPLOG, as an organization, is concerned about women's health issues and recognized that the FDA's violations of its standards and rules in approving Mifeprex put women's lives and health at risk. It took considerable time, energy, and resources to draft the 92-page petition and the 30-page response to comments letter, in addition to compiling and analyzing supporting sources and studies. This effort caused AAPLOG to divert limited time, energy, and resources from its other priorities and routine functions.

42. Similarly, AAPLOG submitted another Citizen Petition in 2019 challenging the FDA's 2016 major changes to the chemical abortion drug regimen, which I also co-authored. It also took considerable time, energy, and resources to draft the 26-page petition, in addition to compiling and analyzing supporting

sources and studies. This effort caused AAPLOG to divert limited time, energy, and resources from its other priorities and routine functions.

43. Because abortion activists continue to file their own citizen petitions and letters with the FDA asking the agency to eliminate all protections for women and girls who take chemical abortion drugs, and knowing the Biden administration's relentless, politicized efforts to push these drugs throughout the country, AHM and AAPLOG continue to expend considerable time, energy, and resources on its public advocacy and educational activities regarding chemical abortion drugs—to the detriment of other AHM and AAPLOG priorities and functions. This diversion of time, energy, and resources will not cease until the FDA's approval and deregulation of chemical abortion drugs ceases.

44. AHM and AAPLOG members are opposed to being forced to end the life of a human being in the womb for no medical reason. The objections are both ethical and medical as they stem from the purpose of medicine itself, which is to heal and not to electively kill human beings regardless of their location. The FDA's removal of REMS for safe use—which eliminates in-person evaluations and follow-up care—places our member doctors at increased risk of being forced to violate their conscience rights. The FDA's actions could force our members into a situation where they must render treatment to a woman in the emergency department suffering complications from chemical

abortion while she is still carrying a living fetus, and they must perform a D&C to treat her complications—ending the life of a human being.

Executed this November 11, 2022.

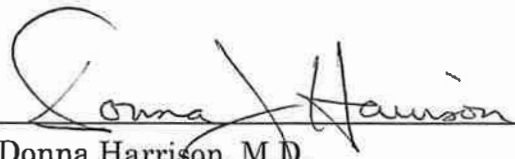
By:  M.D.
Donna Harrison, M.D.

EXHIBIT 5

FDA-Approved Label for Mifepristone

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning. Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)
- Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3). Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

INDICATIONS AND USAGE

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

DOSAGE AND ADMINISTRATION

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

CONTRAINDICATIONS

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

WARNINGS AND PRECAUTIONS

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Regimen
- 2.2 Patient Management Following Misoprostol Administration
- 2.3 Post-treatment Assessment: Day 7 to 14
- 2.4 Contact for Consultation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Infections and Sepsis
- 5.2 Uterine Bleeding
- 5.3 Mifepristone REMS Program
- 5.4 Ectopic Pregnancy
- 5.5 Rhesus Immunization

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

- 7.2 Drugs that May Increase Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

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8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
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- 8.4 Pediatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis [see *Warnings and Precautions (5.1)*].
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding [see *Warnings and Precautions (5.2)*].

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program [see *Warnings and Precautions (5.3)*].

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

Remove any intrauterine device ("IUD") before treatment with MIFEPREX begins [see *Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
 - *Day One: MIFEPREX Administration*
One 200 mg tablet of MIFEPREX is taken in a single oral dose.
 - *Day Two or Three: Misoprostol Administration* (minimum 24-hour interval between MIFEPREX and misoprostol)
Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

Figure 1



2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol [see *Clinical Studies* (14)], discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms [see *Adverse Reactions* (6)].

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion [see *Use in Specific Populations* (8.1)]. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with "MF."

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any of the following conditions:
 - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) [see *Warnings and Precautions* (5.4)]
 - Chronic adrenal failure (risk of acute adrenal insufficiency)
 - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
 - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported [see *Adverse Reactions* (6.2)])
 - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

- Inherited porphyrias (risk of worsening or of precipitation of attacks)
- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device (“IUD”) in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX [see *Boxed Warning*]. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion [see *Boxed Warning*].

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the mifepristone REMS Program, because of the risks of serious complications [see *Warnings and Precautions* (5.1, 5.2)].

Notable requirements of the mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies [see *Contraindications* (4)]. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis [see *Warnings and Precautions* (5.1)]
- Uterine bleeding [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period [see *Warnings and Precautions (5.2)*].

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported

* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortion infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)

Blood and the lymphatic system disorders: anemia

Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)

Psychiatric disorders: anxiety

Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)

Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness

Respiratory, thoracic and mediastinal disorders: shortness of breath

Gastrointestinal disorders: dyspepsia

Musculoskeletal, connective tissue and bone disorders: back pain, leg pain

Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea

General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment [see *Dosage and Administration* (2.3)] to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

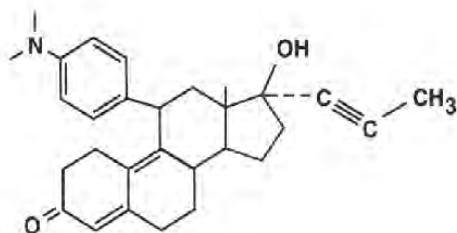
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11 β -[p-(Dimethylamino)phenyl]-17 β -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C₂₉H₃₅NO₂. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for C_{max} after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean C_{max} was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean AUC_{0-∞} was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1 -acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pombe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal)
Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%
<p>* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.</p> <p>** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.</p>		

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and
Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)].

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [see *Warnings and Precautions* (5.2)].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [see *Warnings and Precautions* (5.1, 5.2)].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [see *Warnings and Precautions* (5.3)]. Under the mifepristone REMS Program:
 - Patients must sign a Patient Agreement Form.
 - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever [see *Boxed Warning*].
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to 14 days after taking MIFEPREX [see *Dosage and Administration* (2.3)].
- Explain that
 - prolonged heavy vaginal bleeding is not proof of a complete abortion,
 - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
 - it is recommended that ongoing pregnancy be managed by surgical termination [see *Dosage and Administration* (2.3)]. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

01/2023

<p style="text-align: center;">MEDICATION GUIDE</p> <p style="text-align: center;">Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use)</p>
<p>Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.</p>
<p>What is the most important information I should know about Mifeprex?</p> <p>What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.</p> <p>Be sure to contact your healthcare provider promptly if you have any of the following:</p> <ul style="list-style-type: none"> • Heavy Bleeding. Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C). • Abdominal Pain or "Feeling Sick." If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb). • Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem. <p>If you cannot reach your healthcare provider, go to the nearest hospital emergency room.</p> <p>What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.</p> <p>Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.</p>

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See “What is the most important information I should know about Mifeprex?”

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See “How should I take Mifeprex?” for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to 16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 01/2023

EXHIBIT 6

**Maarit Niinimäki et al., Comparison of
rates of adverse events in adolescent and
adult women undergoing medical abortion:
population register based study**

Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study

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ABSTRACT

Objective To determine the risks of short term adverse events in adolescent and older women undergoing medical abortion.

Design Population based retrospective cohort study.

Setting Finnish abortion register 2000-6.

Participants All women (n=27 030) undergoing medical abortion during 2000-6, with only the first induced abortion analysed for each woman.

Main outcome measures Incidence of adverse events (haemorrhage, infection, incomplete abortion, surgical evacuation, psychiatric morbidity, injury, thromboembolic disease, and death) among adolescent (<18 years) and older (≥18 years) women through record linkage of Finnish registries and genital *Chlamydia trachomatis* infections detected concomitantly with abortion and linked with data from the abortion register for 2004-6.

Results During 2000-6, 3024 adolescents and 24 006 adults underwent at least one medical abortion. The rate of chlamydia infections was higher in the adolescent cohort (5.7% v 3.7%, $P<0.001$). The incidence of adverse events among adolescents was similar or lower than that among the adults. The risks of haemorrhage (adjusted odds ratio 0.87, 95% confidence interval 0.77 to 0.99), incomplete abortion (0.69, 0.59 to 0.82), and surgical evacuation (0.78, 0.67 to 0.90) were lower in the adolescent cohort. In subgroup analysis of primigravid women, the risks of incomplete abortion (0.68, 0.56 to 0.81) and surgical evacuation (0.75, 0.64 to 0.88) were lower in the adolescent cohort. In logistic regression, duration of gestation was the most important risk factor for infection, incomplete abortion, and surgical evacuation.

Conclusions The incidence of adverse events after medical abortion was similar or lower among adolescents than among older women. Thus, medical abortion seems to be at least as safe in adolescents as it is in adults.

INTRODUCTION

Pregnancies among teenagers are mostly unplanned and offer a special challenge to family planning

services. Most of all such pregnancies (up to 82% in the United States) are unintended.¹ The decision to continue or terminate a pregnancy is strongly associated with age. Besides age, being a student or being single are important factors in young women's decisions on abortion.² In the United States, 6% of all abortions are carried out in under 18s.¹ In the United Kingdom, 9.5% of abortions in 2009 were in adolescents.³ Thus abortions among teenagers are common and are an important public health problem.

The medical termination of pregnancy using the antiprogesterone mifepristone and a prostaglandin analogue has been widely established in several countries during the past decade. In 2009, 40% of abortions were medical in the United Kingdom.³ In Sweden and Finland the corresponding figures were 72% and 76%.^{4,5}

Increasing use of medical termination of pregnancy points to a need for appropriate studies to confirm its safety in various target groups. Using nationwide register based data we showed that both medical and surgical abortions are generally safe, with few serious complications when gestation is less than 63 days.⁶ The most common adverse events were haemorrhage and incomplete abortion. However, in that study we did not assess the safety of medical abortion among adolescents.

Data on the safety of medical abortion among adolescents are limited. In a small prospective study, medical abortion was found to be highly effective and well tolerated in adolescents aged 14 to 17 when gestation was less than 56 days. Initially, half of the participants experienced stress and fear, but these emotions improved significantly within the month after abortion.⁷

In the present nationwide study we compared the safety of medical abortion between adolescents and adults. To eliminate the possible influence of previous pregnancies on the outcome of termination of pregnancy, we carried out a subgroup analysis among primigravid women. In addition we assessed the impact of a positive *Chlamydia trachomatis* test result at the time of

abortion on the incidence of infections after abortion—a situation of great clinical relevance to adolescents.

METHODS

From the national abortion register compiled by the National Institute for Health and Welfare we identified all women who had undergone induced abortion in Finland during 2000–6. The study population consisted of women who had had a medical abortion (mifepristone alone or in combination with misoprostol or other prostaglandins) at 20 weeks or less of gestation. We divided the women into two cohorts based on age at the time of abortion: adolescents (<18 years) and adults (≥18 years). To keep the observations independent, we included only the first abortion for women who had more than one during the study period. To assess the potential learning curve in the introduction of medical abortion, we analysed the results in part separately for the first years (2000–3) of its use compared with established use (2004–6). We linked the data with the care register for health institutions (later called the hospital register) and the national infectious diseases register, both compiled by the National Institute for Health and Welfare, and the cause of death register of Statistics Finland. We followed the women for 42 days after the induced abortion and linked all events recorded in the hospital register and cause of death register with the abortion register.

The Finnish national register on induced abortions and sterilisations has been maintained since 1977. In accordance with the current legislation, doctors performing induced abortions are obliged to report cases to the register within one month, using a specific data collection form. In Finland, data on induced abortions are collected from all hospitals and clinics that carry out induced abortions. The register contains data on women having termination of pregnancy. These data include information on pregnancy history, occupation, type of residence, municipality, and marital status. Data on current pregnancy include information on duration of gestation at the time of abortion, indication for abortion, and method of termination.⁵

We have previously described Finnish legislation on induced abortion.⁸ Briefly, current legislation permits termination of pregnancy of up to 20 weeks' gestation

(24 weeks in cases of a medical condition of the fetus) for social, medical, or ethical reasons. A national guideline on the care of women seeking abortion was published in 2001 and updated in 2007.⁹ Based on this guideline all women should be screened for *C trachomatis* and treated if it is present and screened for bacterial vaginosis at the first visit before the termination of pregnancy. Prophylactic antibiotics are not routinely used.

Data collection

All hospitals in Finland are required by law to provide the hospital register with information on inpatient treatment (all hospitals) and outpatient visits (public hospitals). This register contains information on diagnosis (international statistical classification of diseases and related health problems, ICD-10¹⁰) and treatment (Nordic classification of surgical procedures¹¹), as well as the dates of the treatment episodes. To analyse adverse events related to induced abortion we linked information on the study participants in the hospital register for all hospital inpatient episodes and outpatient visits within 42 days after termination of pregnancy with data in the abortion register. We selected diagnoses and codes for surgical procedures in the cohorts for those considered to be of clinical importance.

We divided the complications into eight categories (see box): haemorrhage, infection, incomplete abortion, surgical evacuation, psychiatric morbidity, injury or other reason for surgical operation, thromboembolic disease, and death. The classification was based on that reported in the joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists¹² and modified for this and our previous study.⁶

The cause of death register contains data from death certificates and covers all deaths of Finnish citizens and permanent residents in Finland, classified according to ICD-10 codes. All the early deaths (within 42 days of termination of pregnancy) were classified as direct, indirect, or accidental.¹³

The National Department of Infectious Disease Epidemiology and Control at the National Institute for Health and Welfare collects information on cases of detected *C trachomatis* infections. Since 1997 it has been mandatory for laboratories to report all positive cases to the national infectious diseases register based on the Communicable Diseases Act and Decree of 1987.¹⁴ Since 2004, laboratory notifications have included personal identification numbers, enabling linkage of the data with that in other registries. Since 2004 genital *C trachomatis* has been detected by DNA or RNA testing.¹⁴

Statistical analysis

To assess differences between the groups we used the Mann-Whitney test for age and the χ^2 test for categorical variables. The χ^2 test was also used to calculate the difference in the incidence of adverse events, except for rare ones (psychiatric morbidity, injury, thromboembolic disease, and death) when we used Fisher's

Classification of adverse events

- Haemorrhage—all reported haemorrhage
- Infection—pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections, and septicaemia
- Any reported incomplete abortion
- Surgical evacuation
- Psychiatric morbidity—depression, intoxication, psychoses (ICD-10 codes F10–F48)
- Injury or other reason for surgical operation—all injuries, cervical laceration, uterine perforation, all surgical interventions during follow-up
- Thromboembolic disease—pulmonary embolism, deep vein thrombosis
- Death—death from any cause, pregnancy related death according to the World Health Organization definition

Table 1 Characteristics of the two study cohorts. Values are numbers (percentages) unless stated otherwise

Characteristics	Adolescent cohort (≤ 18 years) (n=3024)	Adult cohort (≥ 18 years) (n=24 006)	P value
Mean (median) age (years), range	16.1 (16.0), 13-17	27.6 (26.0), 18-50	<0.001
Previous pregnancies:			
None	2913 (96.3)	10 474 (43.6)	<0.001
Yes	111 (3.7)	13 532 (56.4)	
Previous deliveries:			
None	2972 (98.3)	12 059 (50.2)	<0.001
Yes	52 (1.7)	11 947 (49.8)	
Previous induced abortions:			
None	3004 (99.3)	19 432 (80.9)	<0.001
Yes	20 (0.7)	4574 (19.1)	
Marital status:			
Married	12 (0.4)	5634 (23.5)	<0.001
Cohabiting	126 (4.2)	4546 (18.9)	
Single	2882 (95.3)	13 785 (57.4)	
Data missing	4 (0.1)	41 (0.2)	
Type of residence:			
Urban	1979 (65.4)	17 977 (74.9)	<0.001
Densely populated	486 (16.1)	2986 (12.4)	
Rural	559 (18.5)	3043 (12.7)	
Duration of gestation (weeks):			
<9	2424 (80.2)	20 143 (83.9)	<0.001
9-12	139 (4.6)	660 (2.7)	
13-16	283 (9.4)	1741 (7.3)	
17-20	171 (5.7)	1151 (4.8)	
Data missing	7 (0.2)	311 (1.3)	
<i>Chlamydia trachomatis</i> positive test result*	99/1749 (5.7)	496/13 547 (3.7)	<0.001

*Data available for 2004-6.

exact test. We used the confidence interval analysis program to calculate the rates of adverse events.¹⁵ For small proportions we used the exact binomial method. The estimated risks of adverse events were determined by logistic regression analyses, and are presented as odds ratios with 95% confidence intervals. Variables that showed statistically significant associations with complications in univariate analysis (type of residence, marital status, duration of gestation, year of abortion, and adolescent or adult cohort) were further entered in multivariate analysis. SPSS 16.0 for Windows was used for the statistical analyses.

RESULTS

During 2000-6, 27 030 women underwent medical abortion between five and 20 weeks of gestation. Of these women, 3024 were younger than 18 (adolescent cohort) and the remaining 24 006 were older (adult cohort). Including only the first induced abortion for each woman during 2000-3, medical abortion was carried out in 1275 (29.3%) adolescents and in 10 459 (31.7%) adults. In 2004-6 the corresponding numbers were 1749 (61.9%) and 13 547 (63.3%).

The two cohorts differed significantly for various characteristics (table 1). The adolescents had fewer previous deliveries and induced abortions and were

more often single and living in a non-urban setting. In both groups, most of the medical abortions (over 80%) were performed before nine weeks of gestation, but the mean duration of gestation was more advanced among adolescents. The incidence of *C trachomatis* infections, diagnosed four weeks before to six weeks after abortion, was higher in the adolescent cohort, as calculated for 2004-6.

Table 2 describes the incidence of adverse events among the two cohorts, as well as among the primigravid women. The adult cohort had a significantly higher incidence of haemorrhage (3690 (15.4%) *v* 386 (12.8%), $P<0.001$), incomplete abortion (2450 (10.2%) *v* 212 (7.0%), $P<0.001$), and surgical evacuation of retained products of conception (3121 (13.0%) *v* 333 (11.0%), $P=0.002$). Odds ratios were calculated for main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation), after adjustment for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion. In the adolescent cohort the adjusted odds ratios were significantly lower for haemorrhage, incomplete abortion, and surgical evacuation than in the adult cohort. In addition, the adult cohort had more participants with adverse events (5535 (23.1%) *v* 575 (19.0%), $P<0.001$).

In the subgroup analysis carried out among the primigravid women, the proportion of women with haemorrhage (1505 (14.4%) *v* 374 (12.8%), $P=0.035$), incomplete abortions (887 (8.5%) *v* 201 (6.9%), $P=0.006$) and a higher overall number of adverse events (2224 (21.1%) *v* 552 (18.9%), $P=0.031$) was significantly higher in the adult cohort. After adjustment for marital status, type of residence, duration of gestation, and year of abortion, the risks for incomplete abortion and surgical evacuation were lower in the primigravid adolescents than in the primigravid adults (table 2).

The incidence of a psychiatric diagnosis was higher among the adolescents in both the cohort and the primigravid cohort, even though the overall numbers were low. Two deaths were reported during the follow-up period. Both of these occurred in adults and were unrelated to the pregnancy (intracranial trauma and melanoma).

The figure shows the results of logistic regression among the primigravid women for risk of main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation). An increased risk of haemorrhage was associated with living in a densely populated area. The risk of bleeding after medical abortion was higher during 2004-6 than during 2000-3. Gestations of 9-12 or 13-16 weeks were associated with a lower risk of haemorrhage than gestations of less than nine weeks. The risk of haemorrhage was also significantly lower in the adolescent cohort.

Advanced duration of gestation (9-12, 13-16, and 17-20 weeks) was associated with an increased risk of infections after abortion (figure). Additionally, being married or cohabiting compared with being single was associated with an increased risk of infection.

Table 2 | Incidence of adverse events in study cohorts for all women (3024 adolescents and 24 006 adults) and for primigravid women (2913 adolescents and 10 474 adults)

Adverse events	Adolescent cohort (<18 years)	% (95% CI)	Adult cohort (≥18 years)	% (95% CI)	P value	Adjusted odds ratio (95%CI)*
All women						
Haemorrhage	386	12.8 (11.6 to 14.0)	3690	15.4 (15.0 to 16.0)	<0.001†	0.87 (0.77 to 0.99)†
Infection	60	2.0 (1.5 to 2.6)	489	2.0 (1.9 to 2.2)	0.742	0.97 (0.73 to 1.30)
Incomplete abortion	212	7.0 (6.1 to 8.0)	2450	10.2 (9.8 to 10.6)	<0.001†	0.69 (0.59 to 0.82)†
Surgical evacuation	333	11.0 (9.9 to 12.1)	3121	13.0 (12.6 to 13.4)	0.002†	0.78 (0.67 to 0.90)†
Psychiatric morbidity	3	0.10 (0.02 to 0.29)	2	NA	0.012†	—
Injury	4	0.13 (0.04 to 0.34)	35	0.15 (0.10 to 0.19)	1.000	—
Thromboembolic disease	2	0.07 (0.01 to 0.24)	26	0.11 (0.07 to 0.15)	0.764	—
Death	0	NA	2	NA	0.392	—
No of adverse events per woman:						
0	2449	81.0 (79.6 to 82.4)	18471	76.9 (76.4 to 77.5)	<0.001†	—
1	488	16.1 (14.8 to 17.4)	4456	18.6 (18.1 to 19.1)		—
2	82	2.7 (2.2 to 3.4)	994	4.1 (3.9 to 4.4)		—
3	5	0.17 (0.05 to 0.39)	83	0.35 (0.27 to 0.42)		—
4	0	NA	2	NA		—
Primigravid women						
Haemorrhage	374	12.8 (11.6 to 14.1)	1505	14.4 (13.7 to 15.0)	0.035†	0.88 (0.78 to 1.00)
Infection	57	2.0 (1.5 to 2.5)	227	2.2 (1.9 to 2.5)	0.486	1.01 (0.75 to 1.37)
Incomplete abortion	201	6.9 (6.0 to 7.9)	887	8.5 (7.9 to 9.0)	0.006†	0.68 (0.56 to 0.81)†
Surgical evacuation	311	10.7 (9.6 to 11.8)	1136	10.8 (10.3 to 11.4)	0.794	0.75 (0.64 to 0.88)†
Psychiatric morbidity	3	0.10 (0.02 to 0.30)	1	NA	0.034†	—
Injury	4	0.14 (0.04 to 0.35)	10	0.10 (0.04 to 0.16)	0.521	—
Thromboembolic disease	2	0.07 (0.01 to 0.25)	10	0.10 (0.04 to 0.16)	1.00	—
Death	0	NA	1	NA	0.391	—
No of adverse events per woman:						
0	2361	81.1 (79.6 to 82.5)	8250	78.8 (78.0 to 79.5)	0.031†	—
1	468	16.1 (14.7 to 17.4)	1838	17.5 (16.8 to 18.3)		—
2	79	2.7 (2.2 to 3.4)	356	3.4 (3.1 to 3.8)		—
3	5	0.17 (0.06 to 0.40)	30	0.29 (0.18 to 0.39)		—
4	0	NA	0	NA		—

NA=not applicable owing to small number of women.

*Adult cohort as reference for all women adjusted for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion; adult cohort as reference for primigravid women adjusted for marital status, type of residence, duration of gestation, and year of abortion.

†Statistically significant.

Also, the risk was higher in the later period (2004-6) than in 2000-3. The risk of infection was similar between the two cohorts.

Advanced duration of gestation was strongly related to the risk of incomplete abortion and surgical evacuation. The risk of incomplete abortion was lower in adolescents (odds ratio 0.69, 95% confidence interval 0.58 to 0.82) than in adults. The risk of surgical evacuation was increased in women living in rural areas and in those who were married or cohabiting. When abortion was carried out in the later period (2004-6) the risk of surgical evacuation was diminished (figure).

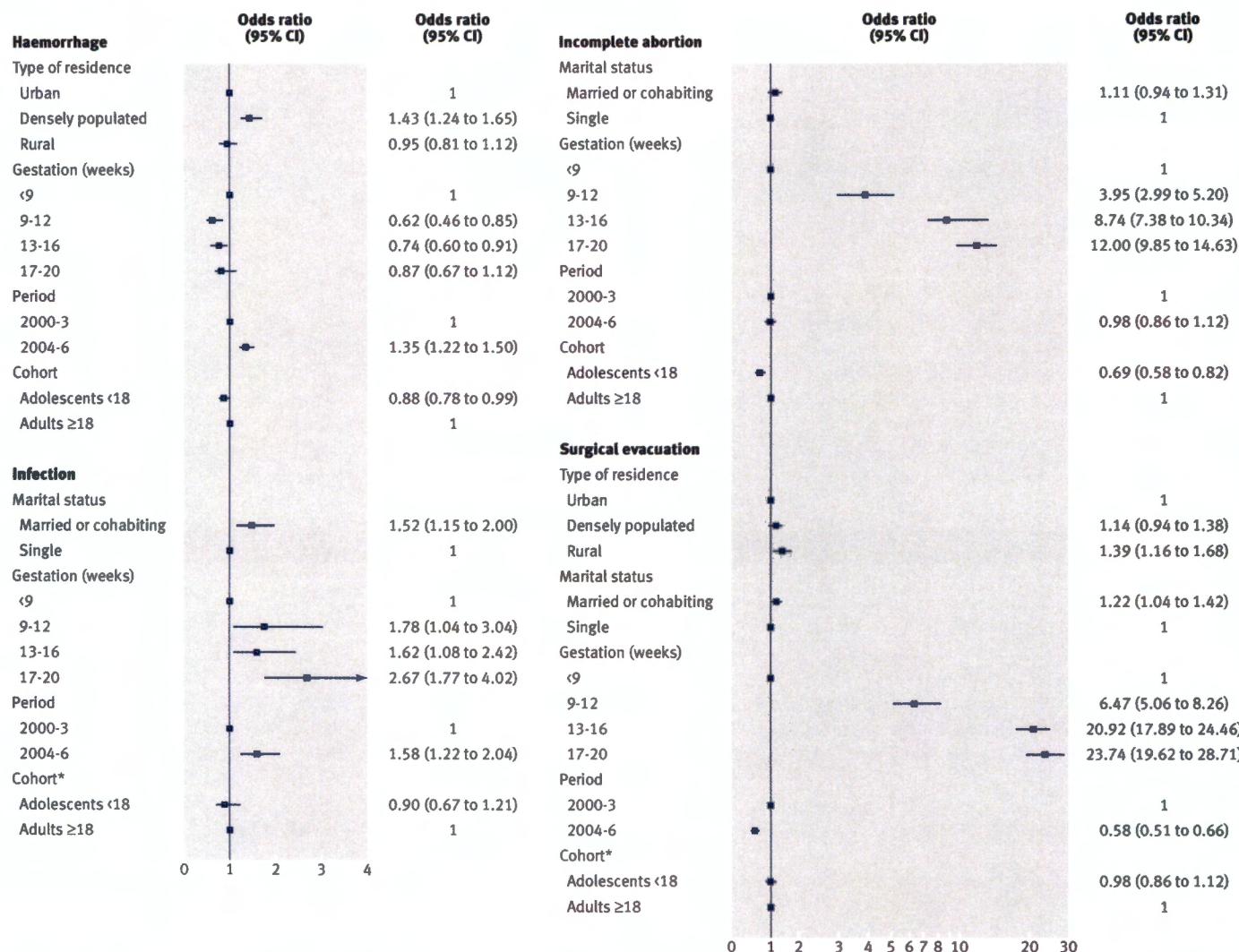
The risk of infections after abortion as a result of concurrent chlamydia infection was assessed among women who underwent abortion during 2004-6. In logistic regression analysis of the whole cohort, the risk of infection after abortion was not associated with concurrent chlamydia infection (1.02, 0.58 to 1.78). Moreover, no significant difference in the rate of infections after abortion emerged between adolescents and

those with a positive test result for *C trachomatis* (data not shown).

DISCUSSION

In the present study the rate of adverse events and complications after medical abortion in adolescents was similar to or lower than that in adults. Various characteristics of the two cohorts differed significantly (table 1), but the risk of adverse events was calculated after adjustment for these factors. This study covered almost all abortions carried out in Finland in all regions and hospitals during a seven year period and thus shows reliable national trends. Earlier studies assessing the completeness of the Finnish abortion register found that 99% of abortions were reported to the register and at least 95% of information matched the medical records.^{16 17}

One limitation of the study is that the registry based data lack detailed information as the diagnoses were made on clinical grounds, and the severity of adverse



Logistic regression analysis of risk factors for main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation) among primigravid women in entire cohort. Results of multivariate analysis are shown unless stated otherwise. Variables showing significance in univariate analysis are included. *Derived from univariate analysis

events may vary substantially. Another drawback is that no conclusions can be made on the effects of abortion beyond the 42 days of follow-up. A further limitation is that data on *C trachomatis* could only be linked with registry data from 2004, when identification numbers were first archived.

More women sought help for bleeding after abortion when gestation was less than nine weeks. This finding parallels that reported in our previous study.⁶ This might be explained partly by the fact that medical abortions at nine weeks or more of gestation are carried out by hospitals, and not on an outpatient basis.⁹ Moreover, an increasing number of these early abortions are carried out at home using self administered misoprostol.

The risk of surgical evacuation of retained products after medical abortion decreased during 2004-6 compared with 2000-3, whereas the number of incomplete abortions remained the same. These findings probably

reflect a learning curve in providing medical abortion. However, the lower number of surgical evacuations occurred at the expense of an increased rate of consultations as a result of uterine bleeding. We took into account the possible bias caused by the differences between the study periods (2000-3 and 2004-6) by adjusting the odds ratios of adverse events by study period.

The rate of infections after abortion was higher (2.0%) than that reported in an earlier review in which medical abortion was assessed (0.9%).¹⁸ The higher figure may in part be a result of the register based nature of the present study—that is, the diagnostic criteria lacked uniformity. In recent reviews, however, the incidence of infections after medical abortion in the second trimester has been estimated to be about 3%.^{19,20} Thus in the present study, concerning pregnancies of up to 20 weeks' duration, the incidence of infections was comparable with that reported in the recent

WHAT IS ALREADY KNOWN ON THIS TOPIC

Teenage pregnancies are mostly unplanned and often result in induced abortion
 Medical abortion is increasingly used, albeit its safety has not been properly assessed among adolescents

WHAT THIS STUDY ADDS

The risk of adverse events (haemorrhage, incomplete abortion, infection) after medical abortion is similar or even lower in adolescent (<18 years) compared with adult women

reviews. The risk of infection was increased when the abortion was carried out in the later period (2004-6). The explanation for this is unclear. The incidence of *C trachomatis* infections in the Finnish population did not change at the same time.¹⁴

C trachomatis is a notable cause of pelvic inflammatory disease. Screening for and treatment of *C trachomatis* can prevent the development of the disease after abortion.²¹ To prevent infection after termination of pregnancy both prophylactic antibiotic therapy for all and screen and treat strategies are in use. In a recent study in the United States, routine provision of doxymycin at the time of medical abortion was associated with a significant reduction in the rate of serious infections.²²

We found no correlation between *C trachomatis* diagnosed at the time of abortion and subsequent infections. In Finland, systematic screening for *C trachomatis* after termination of pregnancy is enforced by national guidelines.⁹ In 2004-6 the national incidence of *C trachomatis* among girls and young women aged 10-19 was 1.7% in Finland,¹⁴ whereas a higher rate of 5.7% was detected in the present adolescent cohort. The results of this study do not rule out the possible association with infections after abortions in the cases of untreated *C trachomatis* infections, or with delayed antibiotic treatment. The present study suggests that by timely screening it is possible to treat the infection before the clinical manifestation.

In the present study psychiatric morbidity was significantly more common among adolescents than among adults, although the number of cases was small. Register based studies are not ideal for studying psychiatric disorders, as only some women seek professional help for mental disorders and only some women with mental disorders are treated in specialised healthcare. In a recent register based Danish study, the risk of a psychiatric disorder in women with no such previously detected disorders was not increased after induced abortion in the first trimester.²³ The risk of psychiatric contact was not, however, significantly affected by age. In a US survey, adolescents were not at increased risk for depression or lower self esteem after abortion than the controls during follow-up.²⁴ The present studies only assessed psychiatric diagnoses during the short follow-up but not possible psychiatric morbidity before abortion. Thus the association of mental disorders and termination of pregnancy among adolescents remains unresolved.

Experience of pain or satisfaction with care could not be studied in the present setting, as these outcomes are not registered in the Finnish abortion register. In a randomised study, women with higher gestational age and first pregnancy seemed to be less satisfied with medical abortion as a result of more pain during the termination.²⁵ The effective treatment of pain must be taken into account when adolescents, predominantly nulliparous women, undergo induced abortion.

Conclusion

The present population based national study provides evidence that medical abortion is not associated with additional risks of adverse events among adolescents in the short term compared with adult women. The data were derived from one country with a homogeneous population but can be generalised to populations with high quality healthcare and easy access to specialist treatment.

The preliminary results of this study were presented at the International Federation of Obstetrics and Gynecology (FIGO) meeting in Cape Town, South Africa October 2009, and in the International Federation of Professional Abortion and Contraception Associates (FIAPAC) meeting in Seville Spain, October 2010 (MN). We thank Aini Bloigu (National Institute for Health and Welfare, Oulu, Finland) for her professional help with the statistics.

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Ethical approval: This study was approved by the ethics committee of the Northern Ostrobothnia Hospital District in October 2005 (No 46/2005). The Ministry of Social Affairs and Health, and Statistics Finland gave permission for the use of confidential personal level data from the registries. The data protection ombudsman was notified about the data linkage before the analyses, as required by national data protection legislation.

Data sharing: No additional data available.

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EXHIBIT 9

ACOG Prac. Bull. No. 181: Prevention of Rh D Alloimmunization



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Prevention of Rh D Alloimmunization

Advances in the prevention and treatment of Rh D alloimmunization have been one of the great success stories of modern obstetrics. There is wide variation in prevalence rates of Rh D-negative individuals between regions, for example from 5% in India to 15% in North America (1). However, high birth rates in low prevalence areas means Rh hemolytic disease of the newborn is still an important cause of morbidity and mortality in countries without prophylaxis programs (1). In such countries, 14% of affected fetuses are stillborn and one half of live born infants suffer neonatal death or brain injury (1). The routine use of Rh D immune globulin is responsible for the reduced rate of red cell alloimmunization in more economically developed countries. First introduced in the 1970s, the postpartum administration of Rh D immune globulin reduced the rate of alloimmunization in at-risk pregnancies from approximately 13–16% to approximately 0.5–1.8% (2, 3). The risk was further reduced to 0.14–0.2% with the addition of routine antepartum administration (2, 3). Despite considerable proof of efficacy, there are still a large number of cases of Rh D alloimmunization because of failure to follow established protocols. In addition, there are new data to help guide management, especially with regard to weak D phenotype women. The purpose of this document is to provide evidence-based guidance for the management of patients at risk of Rh D alloimmunization.

Background

Nomenclature

Nomenclature for red blood cell surface proteins is complex and can be confusing. The red cell membrane contains many anchored surface proteins. Many of these proteins are polymorphic and carry different blood groups. A blood group system consists of one or more antigens controlled at a single gene locus, or by two or more closely linked homologous genes with little or no observable recombination between them. Most blood group antigens are glycoproteins, and their specificity is mostly determined either by the oligosaccharide or amino acid sequence. The 30 human blood group system genes have been identified and sequenced, and all the polymorphisms are known (4).

A variety of terminologies has been used to denote human blood groups since their discovery in 1900. In 1980, the International Society of Blood Transfusion

established a Working Committee to devise and maintain a genetically-based numerical terminology for red cell surface antigens. The numerical terminology was devised for computer storage of information on blood groups antigens and to provide a framework for genetic classification. The numerical terminology is not suitable for everyday communication, which has led to a variety of alternative names being used for some blood group antigens. In an attempt to introduce some uniformity, a recommended list of alternative names for antigens is available through the International Society of Blood Transfusion (4). In most cases the name or symbol is identical to that originally published, but in a few cases the more commonly used name is provided, as with ABO and Rh. Specific subtypes or polymorphisms use a second designation (eg, Rh D, Rh C, Rh E). This document uses the designation Rh D to signify the erythrocyte antigen. Women who carry the Rh D antigen are identified as Rh D positive. Those who do not carry the Rh D



antigen are identified as Rh D negative. Details regarding the nomenclature for partial D or weak D antigens are described as follows (see “How should a weak D blood type be interpreted and what management should be undertaken?”). The frequency of the Rh D-negative phenotype is most common in individuals of European and North American descent (15–17%), is comparatively decreased in the regions of Africa and India (3–8%), and is rarest in Asia (0.1–0.3%) (1, 5). The immune globulin used specifically to bind the Rh D antigen is referred to as Rh D immune globulin or anti-D immune globulin. Alloimmunization refers to an immunologic reaction against foreign antigens that are distinct from antigens on an individual’s cells. In this case, it refers to the maternal formation of antibodies against fetal Rh D. Fetal–maternal hemorrhage is the term used to identify varying amounts of fetal cells in the maternal circulation from small interruptions at the fetal–maternal placental interface (6).

Causes of Rh D Alloimmunization

Rh D alloimmunization occurs when a Rh D-negative woman is exposed to red cells expressing the Rh D antigen. Although the fetal and maternal circulations are separate, there is often some antenatal mixing of fetal and maternal blood, even in asymptomatic women. Events such as miscarriage, ectopic pregnancy, antenatal bleeding, and delivery, as well as procedures such as chorionic villus sampling, amniocentesis, pregnancy-related uterine curettage, and surgical treatment of ectopic pregnancy can lead to maternal exposure to fetal red blood cells and, consequently, Rh D alloimmunization (Box 1). Between 3% and 11% of women with threatened abortion in the first trimester, and approximately 45% giv-

ing birth in the third trimester, have a fetal–maternal hemorrhage (7, 8). The volume of fetal–maternal hemorrhage leading to Rh D alloimmunization can be as small as 0.1 mL or as large as 30 mL (7, 8).

Fetal–maternal hemorrhage also may take place in the first and second trimesters in association with spontaneous pregnancy loss or uterine instrumentation (eg, dilation and curettage or evacuation). The risk of Rh D alloimmunization is estimated to be 1.5–2% in susceptible women after spontaneous miscarriage and 4–5% after dilation and curettage (3, 7). There are insufficient data from studies that evaluated the efficacy of administration of anti-D immune globulin after spontaneous miscarriage and, although alloimmunization appears rare, it is possible and recommendations continue to include administration of anti-D immune globulin after such losses (3, 9, 10). Ectopic pregnancy also may lead to Rh D alloimmunization, although data regarding the probability are lacking. Until further evidence is available, expert advice continues to recommend administration of anti-D immune globulin within 72 hours of suspected breach of the choriodecidual space (9).

Historically, chorionic villus sampling has been estimated to carry a 14% risk of fetal–maternal hemorrhage of 0.6 mL or more (11). Later studies corroborate these earlier findings and continue to support the administration of anti-D immune globulin to Rh D-negative women who have chorionic villus sampling (12, 13). Traditionally, amniocentesis led to a 2–6% rate of fetal–maternal hemorrhage, even if the placenta was not traversed (14, 15). Recent studies suggest the rate of fetal–maternal hemorrhage may be lower than previously thought but not negligible (16, 17) and alloimmunization is possible. Similarly, other invasive procedures such as cordocentesis also can cause fetal–maternal hemorrhage (16) and warrant anti-D immune globulin prophylaxis. Although not invasive, external cephalic version (regardless of success) is associated with a 2–6% risk of fetal–maternal hemorrhage and anti-D immune globulin is indicated for unsensitized Rh D-negative patients (18, 19).

Box 1. Potential Sensitizing Events in Rh D-Negative Women in Pregnancy ↵

- Chorionic villus sampling, amniocentesis, cordocentesis
- Threatened miscarriage or miscarriage
- Ectopic pregnancy
- Evacuation of molar pregnancy
- Therapeutic termination of pregnancy
- Antepartum hemorrhage
- Abdominal trauma
- Intrauterine fetal death
- External cephalic version
- Delivery

Anti-D Immune Globulin to Prevent Alloimmunization

Anti-D immune globulin is extracted by cold alcohol fractionation from plasma donated by individuals with high-titer anti-D immune globulin G antibodies. Original work in the 1960s noted maternal sensitization to fetal Rh-positive blood could be prevented by administering anti-D immune globulin. A prophylactic dose of 300 micrograms of anti-D immune globulin can prevent Rh D alloimmunization after exposure to up to 30 mL of Rh D-positive fetal whole blood or 15 mL of fetal red



blood cells (20). Subsequently anti-D immune globulin became more widely available and a single dose given to susceptible Rh D-negative women within 72 hours of delivery reduced the rate of Rh D alloimmunization by 80–90% (7, 21, 22). However, it became clear that asymptomatic fetal–maternal hemorrhage during the third trimester triggered alloimmunization in 2% of at-risk women before delivery. This rate was shown to be reduced to less than 0.2% with routine antenatal administration of anti-D immune globulin at 28 weeks of gestation (7).

In the United States, a recommendation for the administration of anti-D immune globulin was introduced in the 1970s. The current practice of administering a single antenatal dose of 300 micrograms of anti-D immunoglobulin at 28 weeks of gestation followed by a second dose after birth when newborn Rh D typing has identified the infant as Rh positive, based on recommendations from a conference at McMaster University in 1977, is associated with less than a 0.2% rate of Rh alloimmunization (7, 23). In the United Kingdom, recommendations have differed somewhat from those in the United States in that antenatal Rh D immune globulin using different doses may be given as two injections at 28 weeks of gestation and at 34 weeks of gestation, or as a single administration at 28 weeks of gestation (24, 25). There is no trial comparing the two-dose regimens with a single dose, and no evidence of a difference in efficacy between these regimens (24). However, an observational study from the United Kingdom noted better adherence with the single-dose compared with the two-dose protocol (26). There is also potential cost reduction with a single dose (27). Thus, there are no compelling data indicating a change from the single-dose procedure currently used in the United States to the two-dose regimen.

Although administration of anti-D immune globulin at 28 weeks of gestation is highly effective, pharmacokinetic studies suggest that levels of anti-D vary between patients and some may not have adequate anti-D levels at delivery (28). In the past, some authorities advised giving a second dose of Rh D immune globulin in women who have not given birth 12 weeks after receiving their antenatal dose (29). However, the vast majority of women who give birth more than 12 weeks after receiving antenatal Rh D immune globulin do not become alloimmunized. Because of this low risk of alloimmunization and the fact that 40% of infants of Rh D-negative women will be Rh D negative, most guidelines do not recommend that a second dose of anti-D immune globulin be given until after delivery when newborn Rh D typing becomes available. Additional anti-D immune globulin is needed to prevent

alloimmunization for exposures larger than 30 mL of Rh D-positive fetal whole blood. Rarely, in 2–3 per 1,000 deliveries, a fetal–maternal hemorrhage may be greater than 30 mL (6, 7). For this reason, Rh D-negative women who give birth to Rh D-positive infants should undergo additional testing to assess the volume of fetal–maternal hemorrhage and guide the amount of Rh D immune globulin required to prevent alloimmunization (5, 25, 30, 31). It is advised that all women undergo such screening after delivery because a policy of only screening deliveries with high-risk conditions for excess fetal–maternal hemorrhage, such as abruptio placentae or manual removal of the placenta, will fail to identify a large number of cases requiring more than the standard postpartum dose of Rh D immune globulin (32).

Screening for fetal–maternal hemorrhage in routine situations typically begins with the rosette fetal red blood cell assay. The erythrocyte rosette screen is a sensitive, qualitative test that can detect greater than 2 mL of fetal whole blood in the maternal circulation (32). The rosette test is performed by incubation of a maternal blood sample with Rh immunoglobulin that will bind fetal Rh D-positive red blood cells, followed by the addition of enzyme-treated reagent indicator red blood cells. Rh D-positive fetal red blood cells present in maternal circulation result in forming aggregates (rosettes) that can be visualized by light microscopy. A positive rosette test should be followed with a method to determine the percentage of fetal red blood cells in maternal circulation, such as the Kleihauer–Betke test or flow cytometry. The Kleihauer–Betke acid elution test relies on the principle that fetal red blood cells contain mostly fetal hemoglobin F, which is resistant to acid elution, whereas adult hemoglobin is acid sensitive. Although the Kleihauer–Betke test is inexpensive and requires no special equipment, it lacks standardization and precision, and may not be accurate in conditions in which the mother has a coexistent medical condition that is associated with red blood cells containing an increased percentage of hemoglobin F, such as sickle-cell disease and the thalassemias. Flow cytometry is a specialized technique that is an alternative method available in some hospitals for quantification of fetal–maternal hemorrhage, although its use is limited by equipment and staffing costs. Flow cytometry uses monoclonal antibodies to hemoglobin F or the Rh D antigen with quantification of fluorescence, and is highly sensitive and accurate in identifying fetal red blood cells in maternal blood (32). In clinical situations in which fetal–maternal hemorrhage has occurred in a volume that is not covered by the standard 300 microgram dose of Rh immune globulin (greater than 30 mL of fetal whole blood or 15 mL of fetal red cells) additional vials of Rh immune globulin can be administered at one



time (up to eight full vials). These additional doses can be administered intramuscularly at separate sites every 12 hours until the desired dosage has been reached (33, 34). An intravenous Rh immune globulin is available that also may be used in these cases and provides more comfort for the patient (34).

Because Rh D immune globulin is obtained from human plasma, there is a theoretical risk of transmission of viral infection. In the 1990s, it was discovered that immune globulin contaminated with hepatitis C virus had been administered to women from 1977 to 1979 in Ireland and Germany (35). Most of these exposed women showed only slight to moderate hepatic inflammation 17–35 years later (35, 36). A later analysis of samples manufactured between 1991 and 1994 again demonstrated a low potential for transmission of the hepatitis C virus, with 0.59% of potential exposures showing evidence of seroconversion (37). Regardless, because the product is a purified immune globulin, the risk of viral infection from anti-D immune globulin is exceedingly low. Since 1985, all plasma used for the production of anti-D immune globulin has been tested for viral infections, and several fractionation and purification steps, including micropore filtration, are used to remove and inactivate viruses. Other contaminations and inadvertent exposures have not been reported, and anti-D immune globulin has been manufactured without mercury-containing thimerosal since 2001 (38).

Failure to Prevent Rh D Alloimmunization

Rh alloimmunization during pregnancy in Rh D-negative women may still occur. This might be because of a failure of administering antenatal prophylaxis in the third trimester of pregnancy, insufficient dosage or timely administration (within 72 hours) of anti-D immune globulin given after a known sensitizing event during pregnancy (or after birth), or an unrecognized fetal–maternal hemorrhage at some point in the pregnancy (39). In spite of recommendations for immunoprophylaxis, approximately 0.1–0.4% of women at risk become sensitized during pregnancy (22). A recent retrospective study from New Zealand identified reasons for continued cases of sensitization, including omission of immune globulin after a recognized sensitizing event in 41% of cases and administration outside of recommended guidelines in 13% of cases (40). An additional reason for Rh D alloimmunization is the small rate (0.1–0.2%) of spontaneous immunization despite adherence to the recommended prophylaxis protocol (22). These cases most often occur in pregnancies during which there have been no prior overt sensitizing events. In other words, prophylaxis is not 100% effective (41).

Potential Shortage of Anti-D Immune Globulin

Anti-D immune globulin is collected by apheresis from volunteer donors who have high titers of circulating anti-Rh D antibodies. The donated plasma is pooled and fractionated by commercial manufacturers, and anti-D immune globulin is prepared in varying doses. In the 1990s, concerns were raised regarding future supplies of anti-D immune globulin for worldwide demands because the number of potential donors may dwindle (42). At that time, experts in the United Kingdom estimated that supplies of anti-D immune globulin would be inadequate for immunoprophylaxis of all susceptible Rh D-negative women if standard recommendations were followed (43). In Australia in 1995, a shortage prompted importation of anti-D immune globulin. Subsequently, some physicians proposed strictly limiting the dose given for first-trimester indications and discontinuing administration of anti-D immune globulin after external cephalic version (unless fetal–maternal hemorrhage is documented), ectopic pregnancy, or threatened miscarriage (44). Others disagreed, considering it unethical to withhold anti-D immune globulin in any situation. Estimates regarding future needs compared with potential supply in the United States have not been published. No reports of supply shortages of anti-D immune globulin have been published since initial concerns were expressed 20 years ago. Despite these earlier concerns, national guidelines from the United States, United Kingdom, and Canada still recommend routine administration of anti-D immune globulin to all Rh D-negative nonsensitized women in the third trimester, within 72 hours of delivery in women giving birth to a Rh-positive infant, or when a sensitizing event occurs (eg, ectopic pregnancy, external cephalic version, or invasive obstetric procedures such as chorionic villus sampling or amniocentesis) (5, 25, 31).

Other sources of anti-D immune globulin have been explored. There is the potential to generate recombinant Rh D immune globulin, which would alleviate any future shortages of donors. No commercially available, efficacious recombinant products are currently available. Nonetheless, a monoclonal antibody (Roledumab) and a recombinant antibody mixture (Rozrolimupab) are being designed for prevention of hemolytic disease of the newborn and are in phase II clinical trials (45, 46).

Cost Effectiveness of Rh D Prophylaxis Programs

The cost effectiveness of different screening strategies to guide the administration of Rh D immune globulin to Rh D-negative pregnant women in circumstances where fetal–maternal hemorrhage may occur have been mixed.



Strategies of selective administration of Rh D immune globulin depending on partner's blood type have been shown to be cost equivalent to systematic prophylaxis (47, 48). If the Rh type of the partner is not known, and given that immunological typing of the father would probably not be carried out by most clinicians, routine antenatal prophylaxis remains the preferred option (48). Although initial economic analysis of antenatal anti-D immune globulin prophylaxis suggested that it was only cost effective in primigravid women (27, 47), more recent data indicate that prophylactic administration to all women at risk is cost beneficial (48).

Noninvasive determination of fetal Rh status is now possible through the analysis of cell-free DNA in maternal plasma. Up to 40% of Rh D-negative pregnant women will carry an Rh D-negative fetus. In this clinical situation, antenatal anti-D immune globulin administration is unnecessary. Concerns have been raised about the unwarranted exposure of these pregnant women to a plasma-based product (49). Some parts of the world now are using circulating cell-free DNA testing to ascertain the fetal Rh D status and to establish candidates for antenatal anti-D immune globulin prophylaxis (50). Recent retrospective and prospective observational studies have reported that fetal Rh D status determination in the first trimester has a sensitivity greater than 99% and a specificity of greater than 95% (51–53). However, concerns have been noted because of the rate of inconclusive results (range 2–6%), which are influenced by race (52, 53).

Despite the improved accuracy of noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit. Four cost analyses from North America and Europe have shown no economic benefit at current test-cost levels (48, 54–56), whereas a single report from Canada suggested it would be cost effective, although the estimated cost of performing the cell-free DNA was based on a low-cost, high-throughput method (57). As the cost of this technology diminishes, this may become an attractive and cost-effective strategy. However, at current costs, noninvasive assessment of fetal Rh D status is not recommended for routine use at present.

Clinical Considerations and Recommendations

► *Is anti-D immune globulin indicated in a sensitized pregnancy?*

All pregnant women should be tested at the time of the first prenatal visit for ABO blood group and Rh D type and screened for the presence of erythrocyte antibodies.

If anti-D antibody is identified, further history should be obtained and investigation undertaken to determine whether this is immune mediated or passive (as a result of previous injection of anti-D immune globulin). If it is clear that the origin of the anti-D antibodies detected is a previous routine antenatal anti-D immune globulin prophylaxis or anti-D immune globulin given for a potentially sensitizing event, then the woman should continue to be offered anti-D prophylaxis (25). If Rh D antibodies are present because of sensitization, anti-D immune globulin is not beneficial, and management should proceed in accordance with protocols for Rh D-alloimmunized pregnancies (58).

► *How should one deal with the issue of paternity?*

Reliable rates of nonpaternity are difficult to ascertain but a recent review indicates that the mean rate among population studies is approximately 3% (59). Strategies of selective administration of Rh D immune globulin depending on the partner's blood type have been shown to be cost equivalent to systematic prophylaxis (47, 48). If paternity is certain and the father is known to be Rh D negative, antenatal prophylaxis is unnecessary. If the Rh type of the partner is not known, and given that immunological typing of the father would probably not be carried out by most clinicians, routine antenatal prophylaxis remains the preferred option (48). An alternative strategy is to assess fetal RHD genotype with noninvasive testing and only administer Rh D immune globulin if the fetus is Rh D positive. Despite the improved accuracies noted with noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended (48, 54–56).

► *How should a weak D blood type be interpreted, and what management should be undertaken?*

In the past, a woman whose blood was typed as weak D (formerly known as Du) was thought to have blood cells positive for a variant of the Rh D antigen (60). The prevalence of serologic weak D phenotypes varies by race and ethnicity. Serologic weak D phenotypes are the most common D variants detected in Europe and the United States. An estimated 0.2–1.0% of Caucasians inherit *RHD* genes that code for serologic weak D phenotypes and, in the United States, 80% are associated with weak D type 1, 2, or 3 (60). Some of these individuals express reduced numbers of normal Rh D antigens whereas others express partial or abnormal Rh D antigens. It



is possible for the latter group to develop antibodies against the part of the Rh D antigen that they are missing, and several cases of clinically severe Rh D alloimmunization have been reported in weak D phenotype women (60). Accordingly, the American Association of Blood Banks (AABB) recommends that testing for weak D is unnecessary in individuals who will be transfusion recipients of red blood cells (5). This approach categorizes individuals with weak D as Rh D negative for transfusion, and if pregnant, they are considered a candidate for anti-D immune globulin, hence avoiding potential Rh D alloimmunization.

However, the AABB requires that blood donors be assessed for weak D and if detected, the donors are interpreted to be Rh D positive. This policy prevents the transfusion of Rh D-negative individuals with weak D-positive blood, avoiding cases of Rh D alloimmunization. These seemingly contradictory policies likely have helped to avoid potential cases of Rh D alloimmunization. However, it can be extremely confusing for patients and clinicians. For example, the same individual may be variably characterized as Rh D positive or Rh D negative depending upon whether they are a potential donor or recipient and if weak D is or is not assessed (60). This could easily lead to errors and potential cases of Rh D alloimmunization.

An attractive solution to this problem is to perform molecular genetic RHD typing in weak D phenotype individuals as suggested by the Work Group on RHD Genotyping (60). This would allow for consistency in Rh D typing for individuals during their lifetime. In addition, the administration of Rh D immune globulin could be avoided in the Rh D individual with serologic weak D type 1, 2, or 3, because these are not associated with risk of Rh D alloimmunization, which could potentially reduce the need for tens of thousands of units of Rh D immune globulin each year (60). Currently, there is a lack of comprehensive cost-benefit analysis for this clinical approach. Clinicians are advised to administer Rh D immune globulin to patients with weak D blood type in appropriate clinical situations, by the same rationale as that for Rh D typing blood donors, until further scientific and economic studies are available.

► ***Is threatened pregnancy loss an indication for anti-D immune globulin prophylaxis?***

Whether to administer anti-D immune globulin to a patient with threatened pregnancy loss and a live embryo or fetus at or before 12 weeks of gestation is controversial, and no evidence-based recommendation can be made. The Rh D antigen has been reported on fetal erythrocytes as early as 38 days from fertilization

or 7 3/7 weeks of estimated gestational age (61), and fetal-maternal hemorrhage, although rare, has been documented in 3–11% of women with threatened pregnancy loss from 7 weeks to 13 weeks of gestation (7, 8).

Recommendations regarding anti-D immune globulin with threatened miscarriage have been inconsistent. Several national guidelines recommend against giving anti-D immune globulin to women with threatened pregnancy loss, particularly if bleeding stops before 12 weeks of gestation (25, 30, 62). Other guidelines recommend that anti-D immune globulin should be given (as described below) to all Rh D-negative women with a threatened miscarriage or when vaginal bleeding is heavy, repeated, or associated with abdominal pain, particularly if these events occur as gestational age approaches 12 weeks (25, 31). Because of insufficient evidence that a threatened pregnancy loss before 12 weeks of gestation requires anti-D immune globulin, no recommendation can be made at this time.

► ***Should anti-D immune globulin be given in cases of molar pregnancy?***

Although alloimmunization has been reported with hydatidiform mole (63), the risk is unknown. In theory, Rh D alloimmunization should not occur in cases of classic complete molar pregnancy because organogenesis does not occur, and Rh D antigens are probably not present on trophoblast cells, although this theory has been disputed (64–66). In partial and transitional molar pregnancies, however, the embryonic development may cease after erythrocyte production has begun, making maternal exposure to the Rh D antigen possible (67). Given that the diagnosis of partial versus complete molar pregnancy depends on pathologic and cytogenetic evaluations, it is reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation (25, 31).

► ***How much anti-D immune globulin should be given for first- or second-trimester events (eg, spontaneous abortion, therapeutic abortion, ectopic pregnancy) and invasive obstetric procedures (eg, chorionic villus sampling, amniocentesis)?***

Although the optimal dose of anti-D immune globulin for potentially sensitizing events in the first and second trimesters is unknown, because of the smaller fetal red cell mass at these gestations, the recommended dosage is typically less than that used for routine antenatal prophylaxis in the third trimester. At 12 weeks of gestation, the



total fetal–placental blood volume is 3 mL or 1.5 mL of fetal red cells (44). Regardless, this volume is adequate to sensitize some patients, and the risk of Rh D alloimmunization is estimated to be 1.5–2% in susceptible women after spontaneous miscarriage and 4–5% after dilation and curettage (3).

There are no adequate data to support an evidence-based recommendation, and expert opinion varies on whether anti-D immune globulin should be given with a spontaneous abortion. Because of the small volume of fetal blood and the low incidence of alloimmunization, some groups do not recommend prophylactic anti-D immunoglobulin in cases of spontaneous complete miscarriage before 12 weeks of gestation when the uterus is not instrumented (25, 62). Other experts recommend that either 50 micrograms or 120 micrograms of anti-D immune globulin be given after a complete miscarriage during the first 12 weeks of gestation (30, 31). Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first-trimester miscarriage, especially those that are later in the first trimester. If given, a dose of at least 50 micrograms should be administered. Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for their miscarriage should receive Rh D immune globulin prophylaxis. Patients who have a miscarriage after 12 weeks of gestation should receive 300 micrograms of Rh D immune globulin.

Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical. Most consensus guidelines have recommended 50 micrograms or 120 micrograms of anti-D immune globulin up to 12 weeks of gestation (25, 30, 31, 62), and a dose of 300 micrograms after 12 weeks of gestation (31).

Alloimmunization has been reported to occur in 24% of women with a ruptured tubal pregnancy (68). Again, guidelines differ with regard to the recommended dose of anti-D immune globulin up to 12 weeks of gestation, ranging from 50 micrograms to 120 micrograms (25, 30, 31, 62). After 12 weeks of gestation, 300 micrograms Rh D immune globulin is recommended (31). One expert group differentiates whether anti-D immune globulin should be administered depending upon the treatment method used for the unruptured ectopic pregnancy. Without clear evidence to support the distinction, they do not recommend anti-D immune globulin for women who solely receive medical management, but a dose of 50 micrograms is recommended in women who have a surgical procedure to manage an ectopic pregnancy (62). This notwithstanding, until additional data

are available, administration of Rh D immune globulin for all cases of ectopic pregnancy in Rh D-negative women is recommended.

Administration of Rh D immune globulin is recommended with all invasive diagnostic procedures, such as chorionic villus sampling or amniocentesis, in Rh D-negative women when the fetuses could be Rh D positive. Doses from 50 micrograms to 120 micrograms have been recommended before 12 weeks of gestational age (25, 30, 31). For chorionic villus sampling and amniocentesis performed after 12 weeks of gestation, 125 micrograms or 300 micrograms is recommended (30, 31).

► ***Is second- or third-trimester antenatal hemorrhage an indication for anti-D immune globulin prophylaxis?***

In patients with antenatal hemorrhage after 20 weeks of gestation, the risk of Rh D alloimmunization is uncertain. However, consensus guidelines recommend that susceptible women with bleeding receive anti-D prophylaxis (25, 30, 31). Anti-D immune globulin is recommended for Rh D-negative women who experience antenatal hemorrhage after 20 weeks of gestation. Management of the patient with persistent or intermittent antenatal bleeding is complex. The most conservative approach may be to assess the volume of fetal–maternal hemorrhage with a quantitative test (such as the Kleihauer–Betke test). The appropriate amount of Rh D immune globulin then can be administered to cover the estimated volume of fetal–maternal hemorrhage. In cases of chronic or episodic bleeding this approach may need to be repeated. An intuitive but unproven strategy is to monitor the Rh D-negative patient with continuing antenatal hemorrhage with serial indirect Coombs testing for anti-D approximately every 3 weeks. If the result is positive, indicating the persistence of anti-D immune globulin, then theoretically no additional treatment with anti-D immune globulin is necessary. If the Coombs test result is negative, excessive fetal–maternal hemorrhage may have occurred, and a Kleihauer–Betke test should be performed in order to determine the amount of additional anti-D immune globulin necessary. However, the most conservative approach is to administer additional Rh D immune globulin as needed based on the quantity of fetal–maternal hemorrhage with some authorities recommending an estimation of fetal–maternal hemorrhage be carried out at 2-week intervals (25). Finally, it has been proposed in this clinical situation to use cell-free DNA testing to ascertain the fetal Rh D status and, thus, avoid repeated administration of doses of anti-D immune globulin with an Rh D-negative fetus (25).



► ***Is it necessary to repeat antibody screening in patients at 28 weeks of gestation before the administration of anti-D immune globulin?***

Current U.S. Preventive Services Task Force guidelines recommend repeated Rh D antibody testing for all unsensitized Rh D-negative women at 24–28 weeks of gestation, unless the biological father is known to be Rh D negative (grade B recommendation) (69). Consensus guidelines from around the world recommend that a routine antenatal antibody screen should be obtained at 28 weeks of gestation before administration of anti-D immune globulin (25, 30, 31). The primary rationale for repeating the antibody screen is to identify women who have become alloimmunized before 28 weeks of gestation in order to manage their pregnancies properly. The cost effectiveness of routinely repeating the antibody screen has been questioned because of the low incidence of Rh D alloimmunization occurring before 28 weeks of gestation (70). Regardless, routine antibody screening before anti-D immune globulin administration is advised.

► ***How long does the effect of anti-D immune globulin last?***

The median half-life of anti-D immune globulin is 23 days in the third trimester (28). If delivery occurs within 3 weeks of the standard antenatal anti-D immune globulin administration, the postnatal dose may be withheld in the absence of excessive fetal–maternal hemorrhage (29). The same is true when anti-D immune globulin is given for antenatal procedures, such as external cephalic version or amniocentesis, or for third-trimester bleeding. An excessive number of fetal erythrocytes not covered by anti-D immune globulin administration can be assumed to have entered maternal blood if the results of a Kleihauer–Betke test are positive, and an appropriate dose of Rh-immune globulin should be administered.

► ***When should routine antenatal anti-D prophylaxis be given during pregnancy to prevent alloimmunization?***

Studies comparing the routine antenatal administration of anti-D immune globulin to historic controls have shown significant reductions in the incidence of maternal sensitization to the Rh D antigen. Women originally were offered targeted anti-D immunoglobulin with the aim of preventing sensitization after the birth of a Rh-positive infant and after other potentially sensitizing events such as miscarriage, termination of pregnancy, or invasive obstetric procedures. With this approach, the incidence of hemolytic disease of the newborn

was substantially reduced (7). In a meta-analysis of six trials with more than 10,000 women that compared postpartum anti-D immune globulin prophylaxis within 72 hours of birth with no treatment or placebo, anti-D immune globulin greatly lowered the incidence of Rh D alloimmunization 6 months after birth (risk ratio [RR], 0.04; 95% CI, 0.02–0.06), and in a subsequent pregnancy (RR, 0.12; 95% CI, 0.07–0.23) (71). However, because of concerns of alloimmunization occurring before delivery, experts advocated for prophylactic antenatal anti-D immune globulin to be given in the third trimester (7). Several clinical trials have been conducted; however, the studies have been criticized for being of poor quality and varying substantially in study design with many of the studies using historical rather than concurrent controls (72). In a meta-analysis of two randomized controlled trials of 3,902 Rh D-negative women that compared anti-D immune globulin at 28 weeks and 34 weeks of gestation with no antenatal treatment (but all women who delivered a Rh-positive infant received postpartum anti-D immune globulin), there was no clear difference in the incidence of Rh D alloimmunization during pregnancy, after the birth of a Rh-positive infant, or within 12 months after the birth of a Rh-positive infant. No outcome information was available on the incidence of Rh D alloimmunization in a subsequent pregnancy (22). However, methods for performing bias-adjusted meta-analysis, which enables adjustment for differences in quality and design and, thus, allows all available evidence to be synthesized, are available. A meta-regression using these techniques was performed to estimate the association between the observed effectiveness of different anti-D dose regimens (73). In a bias-adjusted meta-analysis of 10 studies, the pooled odds ratio for a reduction of sensitization was estimated as 0.31 (95% CI, 0.17–0.56). The authors interpreted this result as providing strong evidence for the effectiveness of routine antenatal anti-D immune globulin prophylaxis in preventing sensitization of pregnant Rh D-negative women. Prophylactic anti-D immune globulin should be offered to unsensitized Rh D-negative women at 28 weeks of gestation. Following birth, if the infant is confirmed to be Rh D positive, all Rh D-negative women who are not known to be sensitized should receive anti-D immune globulin within 72 hours of delivery.

► ***Is anti-D immune globulin prophylaxis indicated after abdominal trauma in susceptible pregnant women?***

Although the exact risk of Rh D alloimmunization is unknown, abdominal trauma is sometimes associated



with fetal–maternal hemorrhage, which may lead to alloimmunization (74). The efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials. However, authorities agree that anti-D immune globulin should be administered to Rh D-negative women who have experienced abdominal trauma (25, 30, 74). In Rh D-negative pregnant patients who have experienced abdominal trauma, quantification of fetal–maternal hemorrhage should be done to determine the need for additional doses of anti-D immune globulin (74).

► ***Should anti-D immune globulin be given in cases of intrauterine fetal death occurring in the second or third trimester?***

Fetal death occurs in fetal–maternal hemorrhage in up to 13% of cases in which no obvious other cause (eg, hypertensive disease, fetal anomalies) is found (75–77). Rh D alloimmunization has been reported in cases of fetal death from massive fetal–maternal hemorrhage (78), although the contribution of this cause to the overall problem of Rh D alloimmunization is unknown. The efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials. However, because the benefits are thought to outweigh the risk, anti-D immune globulin should be administered to Rh D-negative women who experience fetal death in the second or third trimester. All such cases should be screened for excessive fetal–maternal hemorrhage at the time of diagnosis of fetal death to determine if additional anti-D immune globulin is required (25).

► ***Should administration of anti-D immune globulin be repeated in patients with a pregnancy greater than 40 weeks of gestation?***

Anti-D immune globulin appears to persist for approximately 12 weeks in most patients, based on pharmacokinetic studies using modern assay methods (28). In the past, some authorities advised giving a second dose of Rh D immune globulin to women who have not given birth 12 weeks after receiving their antenatal dose (29). However, the vast majority of women who give birth more than 12 weeks after receiving antenatal Rh D immune globulin do not become alloimmunized. There is insufficient evidence at this time to make a recommendation for or against administering another dose of anti-D immune globulin to a Rh D-negative woman who remains undelivered at 40 weeks of gestation. Current consensus guidelines either have no recommendation (25, 30) or state that a repeat antepartum dose of anti-D immune globulin is generally not required at 40 weeks

of gestation, provided the routine antenatal prophylaxis was given no earlier than 28 weeks of gestation (31).

► ***Should all Rh D-negative women be screened for excessive fetal–maternal hemorrhage after delivery of a Rh D-positive infant?***

The risk of excessive fetal–maternal hemorrhage exceeding 30 mL of Rh D-positive fetal whole blood (the amount covered by the standard 300-microgram dose of anti-D immune globulin) at the time of delivery is approximately 2 to 3 per 1,000 (6, 7). Screening only pregnancies designated as high risk of excessive fetal–maternal hemorrhage, including cases of abruptio placentae, placenta previa, intrauterine manipulation, or fetal death detects only 50% of patients who require additional anti-D immune globulin (79). For this reason, it is recommended that all Rh D-negative women giving birth to Rh D-positive infants undergo additional testing initially with a qualitative screening test (such as the rosette assay) and, if indicated, quantitative testing (such as the Kleihauer–Betke test) to determine the number of doses of Rh D immune globulin required (5, 25, 30, 31).

► ***Should anti-D immune globulin be withheld from a woman undergoing postpartum sterilization?***

Although a primary reason to prevent alloimmunization is to reduce risk in future pregnancies, there are other indications as well. Pregnancies occur despite sterilization procedures, and most are intrauterine. In addition, alloimmunization complicates crossmatching of blood products in the future (80). Thus, Rh D-negative women who are undergoing postpartum tubal sterilization are candidates for treatment with anti-D immune globulin. The downside of this approach is the low cost effectiveness of the strategy because of the low probabilities of sensitization with the just-completed pregnancy, of sterilization failure, and of a need to receive Rh D incompatible blood in the future (81). If an Rh D-negative woman who has had a sterilization procedure does become pregnant later, even with a miscarriage or ectopic pregnancy, she should be offered anti-D immune globulin in a similar manner as women without sterilization.

► ***What should be done if an Rh D-negative patient is discharged without receiving anti-D immune globulin after a potentially sensitizing event?***

The ideal time to administer anti-D immune globulin is within 72 hours of a potentially sensitizing event.



However, volunteers have received a range of partial to complete protection when anti-D immune globulin was given as late as 13 days after exposure (82). The longer prophylaxis is delayed the less it will be protective, but it has been suggested that a patient may still receive some benefit from anti-D immune globulin as late as 28 days postpartum (29, 31).

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- ▶ Prophylactic anti-D immune globulin should be offered to unsensitized Rh D-negative women at 28 weeks of gestation. Following birth, if the infant is confirmed to be Rh D positive, all Rh D-negative women who are not known to be sensitized should receive anti-D immune globulin within 72 hours of delivery.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- ▶ Administration of Rh D immune globulin is recommended with all invasive diagnostic procedures such as chorionic villus sampling or amniocentesis in Rh D-negative women when the fetuses could be Rh D positive.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- ▶ External cephalic version (regardless of success) is associated with a 2–6% risk of fetal–maternal hemorrhage, and anti-D immune globulin is indicated for unsensitized Rh D-negative patient.
- ▶ It is reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation.
- ▶ Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first-trimester miscarriage, especially those that are later in the first trimester.
- ▶ Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for

their miscarriage should receive Rh D immune globulin prophylaxis.

- ▶ Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical.
- ▶ Administration of Rh D immune globulin for all cases of ectopic pregnancy in Rh D-negative women is recommended.
- ▶ Anti-D immune globulin is recommended for Rh D-negative women who experience antenatal hemorrhage after 20 weeks of gestation.
- ▶ Anti-D immune globulin should be administered to Rh D-negative women who have experienced abdominal trauma.
- ▶ Anti-D immune globulin should be administered to Rh D-negative women who experience fetal death in the second or third trimester.

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The MEDLINE database, the Cochrane Library, and ACOG’s own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1980 and February 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used. Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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EXHIBIT 10

ACOG Prac. Bull. 193 Ectopic-Pregnancy



The American College of
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WOMEN'S HEALTH CARE PHYSICIANS

INTERIM UPDATE

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 193, MARCH 2018

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Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the Committee on Practice Bulletins—Gynecology in collaboration with Kurt T. Barnhart, MD, MSCE; and Jason M. Franasiak, MD, TS (ABB).

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to clarify the guidance on the assessment of hCG levels after uterine aspiration in women with a pregnancy of unknown location.

Tubal Ectopic Pregnancy

Ectopic pregnancy is defined as a pregnancy that occurs outside of the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube. Most cases of tubal ectopic pregnancy that are detected early can be treated successfully either with minimally invasive surgery or with medical management using methotrexate. However, tubal ectopic pregnancy in an unstable patient is a medical emergency that requires prompt surgical intervention. The purpose of this document is to review information on the current understanding of tubal ectopic pregnancy and to provide guidelines for timely diagnosis and management that are consistent with the best available scientific evidence.

Background

Epidemiology

According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies (1). However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992 (1). Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality (2). The prevalence of ectopic pregnancy among women presenting to an emergency department with first-trimester vaginal bleeding, or abdominal pain, or both, has been reported to be as high as 18% (3).

Etiology

The fallopian tube is the most common location of ectopic implantation, accounting for more than 90% of cases (4). However, implantation in the abdomen (1%), cervix (1%), ovary (1–3%), and cesarean scar (1–3%)

can occur and often results in greater morbidity because of delayed diagnosis and treatment (4). An ectopic pregnancy also can co-occur with an intrauterine pregnancy, a condition known as heterotopic pregnancy. The risk of heterotopic pregnancy among women with a naturally achieved pregnancy is estimated to range from 1 in 4,000 to 1 in 30,000, whereas the risk among women who have undergone in vitro fertilization is estimated to be as high as 1 in 100 (5, 6).

Risk Factors

One half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors (3). Women with a history of ectopic pregnancy are at increased risk of recurrence. The chance of a repeat ectopic pregnancy in a woman with a history of one ectopic pregnancy is approximately 10% (odds ratio [OR] 3.0; 95% CI, 2.1–4.4). In a woman with two or more prior ectopic pregnancies, the risk of recurrence increases to more than 25% (OR, 11.17; 95% CI, 4.0–29.5) (3). Other important risk factors for ectopic pregnancy include previous damage to the fallopian tubes, factors secondary to ascending pelvic infection, and prior pelvic or fallopian tube surgery (3, 7). Among women who become pregnant through the use of assisted reproductive technology, certain factors such as tubal factor infertility and multiple

embryo transfer are associated with an increased risk of ectopic pregnancy (8, 9). Women with a history of infertility also are at increased risk of ectopic pregnancy independent of how they become pregnant (7). Other less significant risk factors include a history of cigarette smoking and age older than 35 years (7).

Women who use an intrauterine device (IUD) have a lower risk of ectopic pregnancy than women who are not using any form of contraception because IUDs are highly effective at preventing pregnancy. However, up to 53% of pregnancies that occur with an IUD in place are ectopic (10). Factors such as oral contraceptive use, emergency contraception failure, previous elective pregnancy termination, pregnancy loss, and cesarean delivery have not been associated with an increased risk of ectopic pregnancy (3, 7, 11, 12).

Clinical Considerations and Recommendations

► *How is an ectopic pregnancy diagnosed?*

The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.

Women with clinical signs and physical symptoms of a ruptured ectopic pregnancy, such as hemodynamic instability or an acute abdomen, should be evaluated and treated urgently. Early diagnosis is aided by a high index of suspicion. Every sexually active, reproductive-aged woman who presents with abdominal pain or vaginal bleeding should be screened for pregnancy, regardless of whether she is currently using contraception (13, 14). Women who become pregnant and have known significant risk factors should be evaluated for possible ectopic pregnancy even in the absence of symptoms.

Transvaginal Ultrasonography

Ultrasonography can definitively diagnose an ectopic pregnancy when a gestational sac with a yolk sac, or embryo, or both, is noted in the adnexa (15, 16); however, most ectopic pregnancies do not progress to this stage (15). The ultrasound findings of a mass or a mass with a hypoechoic area that is separate from the ovary should raise suspicion for the presence of an ectopic pregnancy; however, its positive predictive value is only 80% (15) because these findings can be confused with pelvic structures, such as a paratubal cyst, corpus luteum, hydrosalpinx, endometrioma, or bowel. Although an early intrauterine gestational sac may be visualized as early as 5 weeks of gestation (17), definitive ultrasound evidence of an intrauterine pregnancy includes visual-

ization of a gestational sac with a yolk sac or embryo (16). Visualization of a definitive intrauterine pregnancy eliminates ectopic pregnancy except in the rare case of a heterotopic pregnancy. Although a hypoechoic “sac-like” structure (including a “double sac sign”) (18) in the uterus likely represents an intrauterine gestation, it also may represent a pseudogestational sac, which is a collection of fluid or blood in the uterine cavity that is sometimes visualized with ultrasonography in women with an ectopic pregnancy (19, 20).

Serum Human Chorionic Gonadotropin Measurement

Measurement of the serum hCG level aids in the diagnosis of women at risk of ectopic pregnancy. However, serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient’s history, symptoms, and ultrasound findings (21, 22). Accurate gestational age calculation, rather than an absolute hCG level, is the best determinant of when a normal pregnancy should be seen within the uterus with transvaginal ultrasonography (23, 24). An intrauterine gestational sac with a yolk sac should be visible between 5 weeks and 6 weeks of gestation regardless of whether there are one or multiple gestations (25, 26). In the absence of such definitive information, the serum hCG level can be used as a surrogate for gestational age to help interpret a nondiagnostic ultrasonogram.

The “discriminatory level” is the concept that there is a hCG value above which the landmarks of a normal intrauterine gestation should be visible on ultrasonography. The absence of a possible gestational sac on ultrasound examination in the presence of a hCG measurement above the discriminatory level strongly suggests a nonviable gestation (an early pregnancy loss or an ectopic pregnancy). In 50–70% of cases, these findings are consistent with an ectopic pregnancy (27–29). However, the utility of the hCG discriminatory level has been challenged (24) in light of a case series that noted ultrasonography confirmation of an intrauterine gestational sac on follow-up when no sac was noted on initial scan and the serum hCG level was above the discriminatory level (30–32). If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue (24, 32). Women with a multiple gestation have higher hCG levels than those with a single gestation at any given gestational age and may have hCG levels above traditional discriminatory hCG levels before ultrasonography recognition (24).

Trends of Serial Serum Human Chorionic Gonadotropin

A single hCG concentration measurement cannot diagnose viability or location of a gestation. Serial hCG concentration measurements are used to differentiate normal from abnormal pregnancies (21, 22, 33, 34). When clinical findings suggest an abnormal gestation, a second hCG value measurement is recommended 2 days after the initial measurement to assess for an increase or decrease. Subsequent assessments of hCG concentration should be obtained 2–7 days apart, depending on the pattern and the level of change.

In early pregnancy, serum hCG levels increase in a curvilinear fashion until a plateau at 100,000 mIU/mL by 10 weeks of gestation. Guidelines regarding the minimal increase in hCG for a potentially viable intrauterine pregnancy have become more conservative (ie, slower increase) (21, 22) and have been demonstrated to be dependent on the initial value (35). There is a slower than expected increase in serum hCG levels for a normal gestation when initial values are high. For example, the expected rate of increase is 49% for an initial hCG level of less than 1,500 mIU/mL, 40% for an initial hCG level of 1,500–3,000 mIU/mL, and 33% for an initial hCG level greater than 3,000 mIU/mL (35). In early pregnancy, an increase in serum hCG of less than a minimal threshold in 48 hours is suspicious of an abnormal pregnancy (ectopic or early pregnancy loss) because 99% of normal intrauterine pregnancies will have a rate of increase faster than this minimum. However, even hCG patterns consistent with a growing or resolving gestation do not eliminate the possibility of an ectopic pregnancy (36).

Decreasing hCG values suggest a failing pregnancy and may be used to monitor spontaneous resolution, but this decrease should not be considered diagnostic. Approximately 95% of women with a spontaneous early pregnancy loss will have a decrease in hCG concentration of 21–35% in 2 days depending on initial hCG levels (34). A woman with decreasing hCG values and a possible ectopic pregnancy should be monitored until nonpregnant levels are reached because rupture of an ectopic pregnancy can occur while levels are decreasing or are very low.

Pregnancy of Unknown Location

A pregnant woman without a definitive finding of an intrauterine or ectopic pregnancy on ultrasound examination has a “pregnancy of unknown location” (37). A pregnancy of unknown location should not be considered a diagnosis, rather it should be treated as a transient state and efforts should be made to establish a definitive diag-

nosis when possible (16). A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management (22, 37). Follow-up to confirm a diagnosis of ectopic pregnancy in a stable patient, especially at first clinical encounter, is recommended to eliminate misdiagnosis and to avoid unnecessary exposure to methotrexate, which can lead to interruption or teratogenicity of an ongoing intrauterine pregnancy (16, 38, 39). The first step is to assess for the possibility that the gestation is advancing.

When the possibility of a progressing intrauterine gestation has been reasonably excluded, uterine aspiration can help to distinguish early intrauterine pregnancy loss from ectopic pregnancy by identifying the presence or absence of intrauterine chorionic villi. Choosing the appropriate time and intervention should be done through shared decision making, incorporating the patient’s values and preferences regarding maternal risk and the possibility of interrupting a progressing pregnancy. If chorionic villi are found, then failed intrauterine pregnancy is confirmed and no further evaluation is necessary. If chorionic villi are not confirmed, hCG levels should be monitored, with the first measurement taken 12–24 hours after aspiration. A plateau or increase in hCG postprocedure suggests that evacuation was incomplete or there is a nonvisualized ectopic pregnancy, and further treatment is warranted. Although the change at which hCG is considered to have plateaued is not precisely defined, it would be reasonable to consider levels to have plateaued if they have decreased by less than 10–15%. Large decreases in hCG levels are more consistent with failed intrauterine pregnancy than ectopic pregnancy. In two small series of women undergoing uterine aspiration for pregnancy of unknown location, nearly all women with a decrease in hCG levels of 50% or greater within 12–24 hours after aspiration had failed intrauterine pregnancies (29, 40). Patients with a decrease in hCG of 50% or greater can be monitored with serial hCG measurements, with further treatment reserved for those whose levels plateau or increase, or who develop symptoms of ectopic pregnancy. Management of patients with an hCG decrease of less than 50% should be individualized, as while failed intrauterine pregnancy is more frequent, ectopic pregnancy risk is appreciable. One study (29) noted 55.6% of patients with ectopic pregnancies had an hCG decrease of more than 10%, 23.5% had a decrease of more than 30%, and 7.1% had a decrease of more than 50%. In a series of patients who had an initial decrease of hCG levels between 15% and 50% 12–24 hours after office uterine aspiration for pregnancy

of unknown location who were monitored with serial hCG measurement, 3 of 46 patients had rising or plateauing hCG levels necessitating treatment for ectopic pregnancy (41). The other patients had resolving hCG levels, and were presumed to have failed intrauterine pregnancies. Patients with an hCG decline between 15% and 50% 12–24 hours after aspiration require at least close follow-up with serial hCG measurement, with consideration of treatment for ectopic pregnancy based on clinical factors such as plateau or increase in hCG, development of symptoms, or high clinical suspicion or strong risk factors for ectopic pregnancy (29, 40, 41).

There is debate among experts about the need to determine pregnancy location by uterine aspiration before providing methotrexate (42, 43). Proponents cite the importance of confirming the diagnosis to avoid unnecessary exposure to methotrexate and to help guide management of the current pregnancy and future pregnancies (37, 42). Arguments against the need for a definitive diagnosis include concern about the increased risk of tubal rupture because of delay in treatment while diagnosis is established and the increased health-care costs associated with additional tests and procedures (43). However, with close follow-up during this diagnostic phase, the risk of rupture is low. In one large series with serial hCG measurement of women with pregnancies of unknown location, the risk of rupture of an ectopic pregnancy during surveillance to confirm diagnosis was as low as 0.03 % among all women at risk and as low as 1.7% among all ectopic pregnancies diagnosed (22). In addition, presumptive treatment with methotrexate has not been found to confer a significant cost savings or to decrease the risk of complications (44). The choice of performing a uterine aspiration before treatment with methotrexate should be guided by a discussion with the patient regarding the benefits and risks, including the risk of teratogenicity in the case of an ongoing intrauterine pregnancy and exposure to methotrexate.

► **Who are candidates for medical management of ectopic pregnancy?**

Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration (45). These patients generally also are candidates for surgical management. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks

of each approach. Women who choose methotrexate therapy should be counseled about the importance of follow-up surveillance.

Methotrexate

Methotrexate is a folate antagonist that binds to the catalytic site of dihydrofolate reductase, which interrupts the synthesis of purine nucleotides and the amino acids serine and methionine, thereby inhibiting DNA synthesis and repair and cell replication. Methotrexate affects actively proliferating tissues, such as bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue. Systemic methotrexate has been used to treat gestational trophoblastic disease since 1956 and was first used to treat ectopic pregnancy in 1982 (46). There are no recommended alternative medical treatment strategies for ectopic pregnancy beyond intramuscular methotrexate. Although oral methotrexate therapy for ectopic pregnancy has been studied, the outcomes data are sparse and indicate that benefits are limited (47).

Contraindications

Box 1 lists absolute and relative contraindications to methotrexate therapy (45). Before administering methotrexate, it is important to reasonably exclude the presence of an intrauterine pregnancy. In addition, methotrexate administration should be avoided in patients with clinically significant elevations in serum creatinine, liver transaminases, or bone marrow dysfunction indicated by significant anemia, leukopenia, or thrombocytopenia. Because methotrexate affects all rapidly dividing tissues within the body, including bone marrow, the gastrointestinal mucosa, and the respiratory epithelium, it should not be given to women with blood dyscrasias or active gastrointestinal or respiratory disease. However, asthma is not an exclusion to the use of methotrexate. Methotrexate is directly toxic to the hepatocytes and is cleared from the body by renal excretion; therefore, methotrexate typically is not used in women with liver or kidney disease.

Relative contraindications for the use of methotrexate (Box 1) do not serve as absolute cut-offs but rather as indicators of potentially reduced effectiveness in certain settings. For example, a high initial hCG level is considered a relative contraindication. Systematic review evidence shows a failure rate of 14.3% or higher with methotrexate when pretreatment hCG levels are higher than 5,000 mIU/mL compared with a 3.7% failure rate for hCG levels less than 5,000 mIU/mL (48). Of note, studies often have excluded patients from methotrexate treatment when hCG levels are greater than

Box 1. Contraindications to Methotrexate Therapy ↵**Absolute Contraindications**

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient
- Inability to participate in follow-up

Relative Contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial hCG concentration
- Ectopic pregnancy greater than 4 cm in size as imaged by transvaginal ultrasonography
- Refusal to accept blood transfusion

Modified from Medical treatment of ectopic pregnancy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. *Fertil Steril* 2013;100:638–44.

5,000 mIU/mL based on expert opinion that these levels are a relative contraindication to medical management. Other predictors of methotrexate treatment failure include the presence of an advanced or rapidly growing gestation (as evidenced by fetal cardiac activity) and a rapidly increasing hCG concentration (greater than 50% in 48 hours) (48–50).

► ***What methotrexate regimens are used in the management of ectopic pregnancy, and how do they compare in effectiveness and risk of adverse effects?***

There are three published protocols for the administration of methotrexate to treat ectopic pregnancy: 1) a single-dose protocol (51), 2) a two-dose protocol (52), and 3) a fixed multiple-dose protocol (53) (Box 2). The single-dose regimen is the simplest of the three regimens; however, an additional dose may be required to ensure resolution in up to one quarter of patients (54, 55). The two-dose regimen was first proposed in 2007 in an effort to combine the efficacy of the multiple-dose protocol with the favorable adverse effect profile of the single-dose regimen (55). The two-dose regimen adheres to the same hCG monitoring schedule as the single-dose regimen, but a second dose of methotrexate is administered on day 4 of treatment. The multiple-dose metho-

trexate regimen involves up to 8 days of treatment with alternating administration of methotrexate and folinic acid, which is given as a rescue dose to minimize the adverse effects of the methotrexate.

The overall treatment success of systemic methotrexate for ectopic pregnancy, defined as resolution of the ectopic pregnancy without the need for surgery, in observational studies ranges from approximately 70% to 95% (55). Resolution of an ectopic pregnancy may depend on the methotrexate treatment regimen used and the initial hCG level. However, there is no clear consensus in the literature regarding the optimal methotrexate regimen for the management of ectopic pregnancy. The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.

Single-Dose Versus Multiple-Dose

Observational studies that compared the single-dose and multiple-dose regimens have indicated that although the multiple-dose regimen is statistically more effective (92.7% versus 88.1%, respectively; $P=.035$) (single-dose

Box 2. Methotrexate Treatment Protocols ⇐**Single-dose regimen***

- Administer a single dose of methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Measure hCG level on posttreatment day 4 and day 7
 - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
 - If decrease is less than 15%, readminister methotrexate at a dose of 50 mg/m² intramuscularly and repeat hCG level
 - If hCG does not decrease after two doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Two-dose regimen†

- Administer methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Administer second dose of methotrexate at a dose of 50 mg/m² intramuscularly on day 4
- Measure hCG level on posttreatment day 4 and day 7
 - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
 - If decrease is less than 15%, readminister methotrexate 50 mg/m² intramuscularly on day 7 and check hCG levels on day 11
 - If hCG levels decrease 15% between day 7 and day 11, continue to monitor weekly until reaching nonpregnant levels
 - If the decrease is less than 15% between day 7 and day 11, readminister dose of methotrexate 50 mg/m² intramuscularly on day 11 and check hCG levels on day 14
 - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Fixed multiple-dose regimen‡

- Administer methotrexate 1 mg/kg intramuscularly on days 1, 3, 5, 7; alternate with folinic acid 0.1 mg/kg intramuscularly on days 2, 4, 6, 8
- Measure hCG levels on methotrexate dose days and continue until hCG has decreased by 15% from its previous measurement
 - If the decrease is greater than 15%, discontinue administration of methotrexate and measure hCG levels weekly until reaching nonpregnant levels (may ultimately need one, two, three, or four doses)
 - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Abbreviation: hCG, human chorionic gonadotropin.

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†Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. *Fertil Steril* 2007;87:250-6.

‡Rodi IA, Sauer MV, Gorill MJ, Bustillo M, Gunning JE, Marshall JR, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. *Fertil Steril* 1986;46:811-3.

failure OR, 1.71; 95% CI, 1.04–2.82), the single-dose regimen is associated with a decreased risk of adverse effects (OR, 0.44; 95% CI, 0.31–0.63) (55). However, a more recent systematic review of randomized controlled trials showed similar rates of successful resolution with the single-dose and multiple-dose regimens (relative risk [RR], 1.07; 95% CI, 0.99–1.17) and an increased risk of adverse effects with the multiple-dose protocol (RR, 1.64; 95% CI, 1.15–2.34) (56).

Single-Dose Versus Two-Dose

A systematic review and meta-analysis of three randomized controlled trials showed similar rates of successful resolution for the two-dose and single-dose protocols (RR, 1.09; 95% CI 0.98–1.20) and comparable risk of adverse effects (RR, 1.33; 95% CI, 0.92–1.94) (56). However, in two of the three trials included in the review, the two-dose regimen was associated with greater success among women with high initial hCG levels. In the first trial, there was a nonstatistically significant trend toward greater success for the two-dose regimen in the subgroup with an initial hCG level greater than 5,000 mIU/mL (80.0% versus 58.8%, $P=.279$) (RR, 0.74; 95% CI, 0.47–1.16) (57). The second trial reported a statistically significant higher success rate for the two-dose regimen versus the single-dose regimen in patients with initial serum hCG levels between 3,600 mIU/mL and 5,500 mIU/mL (88.9% versus 57.9%, $P=.03$) (OR 5.80; 95% CI, 1.29–26.2) (58).

► **What surveillance is needed after methotrexate treatment?**

After administration of methotrexate treatment, hCG levels should be serially monitored until a nonpregnancy level (based upon the reference laboratory assay) is reached (51). Close monitoring is required to ensure disappearance of trophoblastic activity and to eliminate the possibility of persistent ectopic pregnancy. During the first few days after treatment, the hCG level may increase to levels higher than the pretreatment level but then should progressively decrease to reach a nonpregnant level (51). Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention (51). Methotrexate treatment failure in patients who did not undergo pretreatment uterine aspiration should raise concern for the presence of an abnormal intrauterine gestation. In these patients, uterine aspiration should be considered before repeat methotrexate administration or surgical manage-

ment, unless there is clear evidence of a tubal ectopic pregnancy. Ultrasound surveillance of resolution of an ectopic pregnancy is not routinely indicated because findings do not predict rupture or time to resolution (59, 60). Resolution of serum hCG levels after medical management is usually complete in 2–4 weeks but can take up to 8 weeks (55). The resolution of hCG levels is significantly faster in patients successfully treated with the two-dose methotrexate regimen compared with the single-dose regimen (25.7+13.6 versus 31.9+14.1 days; $P>.025$) (57).

► **What are the potential adverse effects of systemic methotrexate administration?**

Adverse effects of methotrexate usually are dependent on dose and treatment duration. Because methotrexate affects rapidly dividing tissues, gastrointestinal problems (eg, nausea, vomiting, and stomatitis) are the most common adverse effects after multiple doses. Vaginal spotting is expected. It is not unusual for women treated with methotrexate to experience abdominal pain 2–3 days after administration, presumably from the cytotoxic effect of the drug on the trophoblastic tissue. In the absence of signs and symptoms of overt tubal rupture and significant hemoperitoneum, abdominal pain usually can be managed expectantly by monitoring a woman's hemoglobin level and intraperitoneal fluid amount with transvaginal ultrasonography.

Elevation of liver enzymes is a less commonly reported adverse effect and typically resolves after discontinuing methotrexate use (61). Alopecia also is a rare adverse effect of the low doses used to treat ectopic pregnancy. Cases of pneumonitis also have been reported, and women should be counseled to report any fever or respiratory symptoms to their physicians (62).

► **How should women be counseled regarding the treatment effects of methotrexate?**

Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed. It is important to educate patients about the symptoms of tubal rupture and to emphasize the need to seek immediate medical attention if these symptoms occur. Vigorous activity and sexual intercourse should be avoided until confirmation of resolution because of the theoretical risk of inducing rupture of the ectopic pregnancy. Additionally, practitioners should limit pelvic and ultrasound examinations when possible. Patients should be advised to avoid folic acid supplements, foods

that contain folic acid, and nonsteroidal antiinflammatory drugs during therapy because these products may decrease the efficacy of methotrexate. Avoidance of narcotic analgesic medications, alcohol, and gas-producing foods are recommended so as not to mask, or be confused with, escalation of symptoms of rupture. Sunlight exposure also should be avoided during treatment to limit the risk of methotrexate dermatitis (63).

Before treatment with methotrexate, women should be counseled about the potential for fetal death or teratogenic effects when administered during pregnancy. The product labeling approved by the U.S. Food and Drug Administration recommends that women avoid pregnancy during treatment and for at least one ovulatory cycle after methotrexate therapy (63). Methotrexate is cleared from the serum before the 4–12 weeks necessary for the resolution of the ectopic gestation and ovulation in the next cycle (64, 65). However, there are reports of methotrexate detectable in liver cells 116 days past exposure (66). Limited evidence suggests that the frequency of congenital anomalies or early pregnancy loss is not elevated in women who have become pregnant shortly after methotrexate exposure (66). However, perhaps based on the timing of methotrexate's clearance from the body, some experts continue to recommend that women delay pregnancy for at least 3 months after the last dose of methotrexate (67).

► ***How does methotrexate treatment affect subsequent fertility?***

Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve. A prospective observational study noted no difference in anti-müllerian hormone levels or reproductive outcomes after administration of methotrexate (68). Furthermore, a systematic review of women undergoing fertility treatment found no significant differences in the mean number of oocytes retrieved during the cycles before and after methotrexate administration (69).

► ***Who are candidates for surgical management of ectopic pregnancy?***

In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each

approach. Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

Surgical management is necessary when a patient meets any of the absolute contraindications to medical management listed in Box 1 and should be considered when a patient meets any of the relative contraindications. Surgical management should be employed when a patient who initially elects medical management experiences a failure of medical management. Surgical treatment also can be considered for a clinically stable patient with a nonruptured ectopic pregnancy or when there is an indication for a concurrent surgical procedure, such as tubal sterilization or removal of hydrosalpinx when a patient is planning to undergo subsequent in vitro fertilization.

Surgical management generally is performed using laparoscopic salpingectomy (removal of part or all of the affected fallopian tube) or laparoscopic salpingostomy (removal of the ectopic pregnancy while leaving the affected fallopian tube in situ). Laparotomy typically is reserved for unstable patients, patients with a large amount of intraperitoneal bleeding, and patients in whom visualization has been compromised at laparoscopy.

► ***How do medical management and surgical management of ectopic pregnancy compare in effectiveness and risk of complications?***

Medical management of ectopic pregnancy avoids the inherent risks of surgery and anesthesia. However, compared with laparoscopic salpingectomy, medical management of ectopic pregnancy has a lower success rate and requires longer surveillance, more office visits, and phlebotomy. Randomized trials that compared medical management of ectopic pregnancy with methotrexate to laparoscopic salpingostomy have demonstrated a statistically significant lower success rate with the use of single-dose methotrexate (relative rate for success, 0.82; 95% CI, 0.72–0.94) and no difference with the use of multidose methotrexate (relative rate for success, 1.8; 95% CI, 0.73–4.6) (70). Comparing systemic methotrexate with tube-sparing laparoscopic surgery, randomized trials have shown no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies (70).

Medical management of ectopic pregnancy is cost effective when laparoscopy is not needed to make the diagnosis and hCG values are less 1,500 mIU/mL (71). Surgical management of ectopic pregnancy is more cost

effective if time to resolution is expected to be prolonged, or there is a relatively high chance of medical management failure, such as in cases with high or increasing hCG values or when embryonic cardiac activity is detected (72, 73).

► ***How do salpingostomy and salpingectomy compare in effectiveness and fertility outcomes in the management of ectopic pregnancy?***

The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage. Randomized controlled trials that compared salpingectomy with salpingostomy for the management of ectopic pregnancy have found no statistically significant difference in the rates of subsequent intrauterine pregnancy (RR, 1.04; 95% CI, 0.899–1.21) or repeat ectopic pregnancy (RR, 1.30; 95% CI, 0.72–2.38) (74). In contrast, cohort study findings indicate that salpingostomy is associated with a higher rate of subsequent intrauterine pregnancy (RR, 1.24; 95% CI, 1.08–1.42) but also with an increased risk of repeat ectopic pregnancy (10% versus 4%; RR, 2.27; 95% CI, 1.12–4.58) compared with salpingectomy (74).

In general, salpingectomy is the preferred approach when severe fallopian tube damage is noted and in cases in which there is significant bleeding from the proposed surgical site. Salpingectomy can be considered in cases of desired future fertility when the patient has a healthy contralateral fallopian tube. However, salpingostomy should be considered in patients who desire future fertility but have damage to the contralateral fallopian tube and in whom removal would require assisted reproduction for future childbearing. When salpingostomy is performed, it is important to monitor the patient with serial hCG measurement to ensure resolution of ectopic trophoblastic tissue. If there is concern for incomplete resection, a single prophylactic dose of methotrexate may be considered (45).

► ***Who are candidates for expectant management of diagnosed ectopic pregnancy?***

There may be a role for expectant management of ectopic pregnancy in specific circumstances. Candidates for successful expectant management of ectopic pregnancy should be asymptomatic; should have objective evidence of resolution (generally, manifested by a plateau or decrease in hCG levels); and must be counseled and willing to accept the potential risks, which include tubal rupture, hemorrhage, and emergency surgery. If the initial

hCG level is less than 200 mIU/mL, 88% of patients will experience spontaneous resolution; lower spontaneous resolution rates can be anticipated with higher hCG levels (75). In a single small randomized trial of women with hCG levels less than 2,000 mIU/mL, expectant management was not associated with a statistically significant lower treatment success than single-dose methotrexate for the management of ectopic pregnancy (59% versus 76%, respectively) (RR, 1.3; 95% CI, 0.9–1.8) (76). Reasons for abandoning expectant management include intractable or significantly increased pain, insufficient decrease of hCG levels, or tubal rupture with hemoperitoneum.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach.
- Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient's history, symptoms, and ultrasound findings.
- If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue.
- The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy

should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage.

- ▶ The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.
- ▶ Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention.
- ▶ Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve.
- ▶ There may be a role for expectant management of ectopic pregnancy in specific circumstances.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- ▶ The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.
- ▶ A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management.
- ▶ Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration.
- ▶ After administration of methotrexate treatment, hCG levels should be serially monitored until a non-pregnancy level (based upon the reference laboratory assay) is reached.

- ▶ Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed.

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Tubal ectopic pregnancy. ACOG Practice Bulletin No. 193. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2018; 131:e91–103.

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and September 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

This information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations in practice may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology. The American College of Obstetricians and Gynecologists reviews its publications regularly; however, its publications may not reflect the most recent evidence. Any updates to this document can be found on www.acog.org or by calling the ACOG Resource Center.

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EXHIBIT 11

**Will a doctor be able to tell if you've taken abortion
pills? – Women Help Women**

Will a doctor be able to tell if you've taken abortion pills?

Monday, September 23, 2019 [blog \(/en/blog\)](#)[Share](#)

Can a doctor tell if someone has used abortion pills?



(/en/page/1094/woman-with-laptop-and-mug)

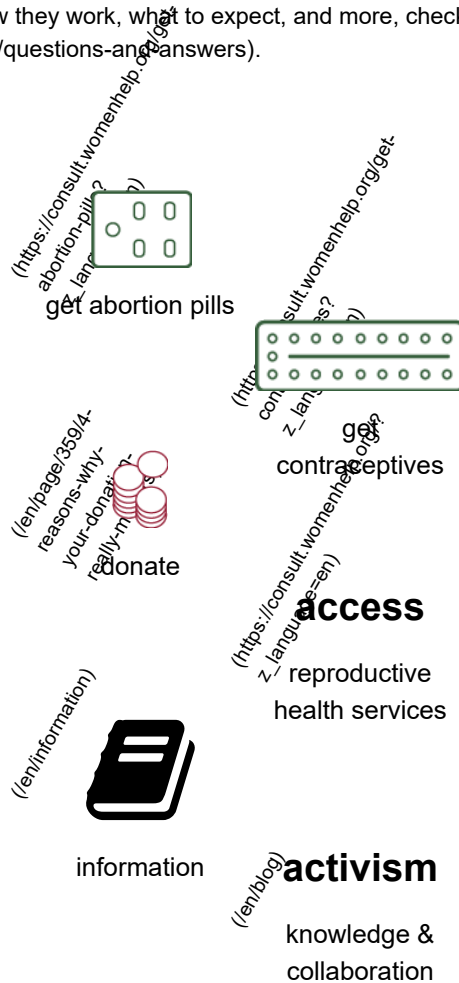
There are many reasons one might choose to take abortion pills, as opposed to seeking abortion care in a clinical setting. Because 90% of US counties (<https://data.guttmacher.org/states/table?state=US&topics=58&dataset=data>) lack an abortion clinic, she may be unable to afford the cost of travel, which also may involve taking one or more days off of work (depending on the abortion regulations in her state), finding childcare, lodging, and more. She may prefer to control where and when she takes the pills, and where she experiences cramping, bleeding (<https://womenhelp.org/en/page/1045/how-much-and-for-how-long-should-you-bleed-after-taking-misoprostol>), and other symptoms. She may not want her abusive partner (<https://womenhelp.org/en/page/976/what-reproductive-coercion-has-to-do-with-abortion-access>), her parents (<https://womenhelp.org/en/page/904/parental-notification-laws-are-toxic-for-young-people-seeking-abortion-care>), or anyone in her life to find out about her pregnancy or her abortion. If this is the case, she will likely be anxious that, even once her abortion is complete (<https://womenhelp.org/en/page/991/how-do-i-know-if-my-medical-abortion-was-successful>), that someone in the future, namely a doctor, will learn that she's had an abortion.

Can a doctor tell if someone has used abortion pills? The answer is no, if they have been taken orally. (If the pills are inserted into the vagina, a doctor may be able to tell if there are traces remaining.) If one took the mifepristone/misoprostol combination, or misoprostol on its own, and she does seek medical care because of complications (<https://consult.womenhelp.org/en/page/416/signs-of-complication>), she does not need to tell a health care provider that she took abortion pills. The symptoms of a miscarriage and a medical abortion are the same, and there are no tests that can prove one has had a medical abortion(s). (<https://nwhn.org/abortion-pills-vs-miscarriage-demystifying-experience/>)

So a doctor can't tell if one has had a medical abortion, and in situations where one fears for her personal safety, or doesn't trust her health care provider with this information, that's a good thing. But if neither of these is the case, it's important to consider why someone would not want her doctor to know her entire medical history, including abortions. Is she holding back this information out of shame? Does she secretly fear that abortion has endangered her fertility? Abortion doesn't impact future fertility, and doctors who traffic in actual medicine know this, and should make sure their patients know it as well.

Abortion stigma (<https://womenhelp.org/en/page/946/abortion-stigma-101-and-how-it-interferes-with-access-to-self-managed-abortion>), or ideas and beliefs about abortion that are medically inaccurate and negative, can result in those who take abortion pills not seeking medical care if they need it, taking the pills incorrectly, or getting the pills from sources that aren't safe, since they don't want anyone to know that they're seeking abortion. Health care providers should not in any way contribute to the perpetuation of abortion stigma; in fact, it's their job to ensure that people get accurate information and medical care regardless of their personal beliefs.

To learn more about about abortion pills, how they work, what to expect, and more, check out Women Help Women's FAQs (<https://consult.womenhelp.org/en/page/377/questions-and-answers>).



(<https://www.facebook.com/womenhelpwomeninternational?ref=hl>)



(<https://twitter.com/WomenHelpOrg>)

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EXHIBIT 12

**How do you know if you have abortion
complications_ @ AidAccess**



AidAccess (/en/)

Get Abortion Pills (/en/i-need-an-abortion)

How do you know if you have abortion complications?

If performed in the first 13 weeks, a medical abortion carries a very small risk of complications. This risk is the same as when a woman has a miscarriage.

What are the possible abortion pill complications and what should you do?

These are the possible complications, their symptoms and treatment:

Heavy bleeding (occurs in less than 1% of medical abortions)

- **Symptom:** Bleeding that lasts for more than 2 hours and soaks more than 2 maxi sanitary pads per hour. Feeling dizzy or light-headed can be a sign of too much blood loss. This is dangerous to your health and must be treated by a doctor.
- **Treatment:** a vacuum aspiration (curettage.) When available, a woman should start taking 2 Misoprostol under the tongue immediately at home before going to the hospital. Very rarely (less than 0.2%) a blood transfusion is needed.

Incomplete abortion

- **Symptoms:** heavy or persistent bleeding and/or persistent severe pain.
- **Treatment:** 2 tablets of Misoprostol or/ and a vacuum aspiration (curettage)

Infection

- **Symptom:** If you have a fever (more than 100.4 degrees Fahrenheit) for more than 24 hours, or you have a fever of more than 102.2 degrees Fahrenheit, there might be an infection that needs treatment.
- **Treatment:** antibiotics and/or vacuum aspiration.

If you think you might have a complication you should go to a doctor immediately. You do not have to tell the medical staff that you tried to induce an abortion; you can tell them that you had a spontaneous miscarriage. Doctors have the obligation to help in all cases and know how to handle a miscarriage.

Miscarriage vs abortion symptoms

The symptoms of a miscarriage and an abortion with pills are exactly the same and the doctor will not be able to see or test for any evidence of an abortion, as long as the pills have completely dissolved. If you used the Misoprostol under the tongue as our protocol recommends, the pills should have dissolved within 30 minutes. If you

took the pills vaginally, you must check with your finger to make sure that they are dissolved. Traces of the pills may be found in the vagina up to four days after inserting them.


Get Abortion Pills (/en/i-need-an-abortion)

Ongoing pregnancy

Less than 1% of women experience ongoing pregnancy.[1] This can be determined by a pregnancy test after 3 weeks or an ultrasound within 10 days. If the medical abortion treatment failed, there is a slight increase in the risk of birth defects such as deformities of the hands or feet and problems with the nerves of the fetus. To treat an ongoing pregnancy, you must repeat a medical or surgical abortion.

[1] "Low-dose Mifepristone Regimens are Effective and Safe for Early Abortion." The Guttmacher Institute.

<https://www.guttmacher.org/journals/ipsrh/2013/07/low-dose-mifepristone-regimens-are-effective-and-safe-early-abortion>

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We answer all of your abortion pill...

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EXHIBIT 13

#AbortionChangesYou_ A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives



Health Communication

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#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives

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#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives

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ABSTRACT

One out of four women in the United States will have an abortion by age 45. While abortion rates are steadily declining in the United States, the rate of medication abortions continues to increase, with 39% of all abortions being medication abortions. Our study is one of the first to analyze women's narratives after having had a medication abortion. Using relational dialectics theory, we conducted a case study of the nonpartisan website, *Abortion Changes You*. Our contrapuntal analysis rendered four sites of dialectical tension found across women's blog posts: *only choice vs. other alternatives*, *unprepared vs. knowledgeable*, *relief vs. regret*, and *silence vs. openness*. Each site of struggle characterized a different noteworthy moment within a woman's medication abortion experience: the decision, the medication abortion process, identity after abortion, and managing the stigmatizing silence before and after the abortion. We discuss theoretical and practical implications about how the larger politicized discourses prevalent within the abortion debate impact the liminality of women who are contemplating a medication abortion and affect their own narrative construction about the medication abortion experience.

One out of four women will undergo an abortion procedure in the United States by age 45 (R. K. Jones & Jerman, 2017), and 862,320 reported abortions occur each year (Jones et al., 2019). Despite its frequency, abortion remains a highly contested and stigmatized biopolitical public health issue in the United States (Altshuler et al., 2017). The historic *Roe v. Wade* case has resulted in two nationalized political movements – Right to Life and Right to Choice – that have juxtaposed stances on the legality of abortion. However, the stigma and shame associated with abortion precede and transcend this historic case. Stormer (2010) concluded that a collective memory of secrets and shame has characterized the topic of abortion since Planned Parenthood's 1955 conference, "Abortion in the United States".

While abortion rates are steadily declining in the U.S. (Jones et al., 2019), the rate of medication abortions continues to increase. In 2000, the U.S. Food and Drug Administration (FDA) approved mifepristone to be used in combination with misoprostol as a form of medication abortion. Since then, the annual number of medication abortions has risen steadily: less than 6% of all abortions in 2001 to 39% of all abortions in 2017 (Jones et al., 2019, 2008). Between 2014–2017, the number of medication abortions provided at facilities other than hospitals increased by 25% (Jones et al., 2019). Presently, over one-third of all reported abortions in the U.S. are medication abortions (Jones et al., 2019). In 2016, the FDA protocol expanded provider eligibility for dispensing mifepristone to women. Thus, abortion provision is transitioning from formalized medical procedures conducted in health care settings

to a protocol where most of the abortion occurs individually at home with limited clinician assistance (Biggs et al., 2019). Given the privatization of abortion provision, research is needed to examine the distinct experiences of women who have undergone this type of abortion. After all, researchers have found that women often elect to have a medication abortion over a surgical abortion because of more privacy, convenience, and the perception of having more control (Newton et al., 2016). However, medication abortion has been found to have a higher complication rate that results in more emergency department visits post-medication abortion compared to post-surgical abortion (Upadhyay et al., 2015).

Medication abortion practices in the U.S. adhere to the following evidence-based guidelines: using mifepristone in combination with a prostaglandin to carry success rates up to 99% for early pregnancy termination with rare occurrence of serious adverse events. However, the focus of this research is on successful terminations, increases in abortion access, and reductions of in-person clinic visits (H. E. Jones et al., 2017). There remains a dearth of research, particularly in the U.S., that examines women's personal experiences with having this type of abortion procedure (e.g., acknowledging their emotions, understanding their self-efficacy with completing the abortion at home, being aware of whether they are adequately informed about the process). To our knowledge, the only study is from Sweden; researchers used semi-structured telephone interviews with 119 women who had a medication abortion (Hedqvist et al., 2016). They found that almost half (43%) experienced more bleeding than expected, and one-

fourth (26%) bled for more than four weeks. In addition, one-third (34%) stated that they received insufficient information about what to expect. Women who had never had an abortion nor had gone through childbirth were more likely to feel misinformed.

Scholars know that the medication abortion process is distinct from surgical abortions, with the features of medication abortion (e.g., lack of medical presence, time required for abortion completion, personal experiences with pain and bleeding) influencing women's perception and satisfaction (Newton et al., 2016). Yet, this research on women's satisfaction with medication abortion is often conflicting (Kimport et al., 2012) and limited (Hedqvist et al., 2016). Given that women increasingly prefer medication abortion over surgical abortion (Newton et al., 2016), the need for studying women's experiences post-medication abortion becomes imperative.

Importance of analyzing unsolicited blogging narratives about one's abortion

To understand women's medication abortion experiences, it is important to study platforms where women engage in unsolicited talk. Unsolicited talk is ideal for collecting formative research that can be studied to explore individual and cultural experiences (Baxter, 2011). First, the audience of these texts is a "generalized other" (Mead, 1982), or culture, rather than a specific individual with whom the author has a relationship (Langellier & Peterson, 2004). The absence of a specific audience encourages narrators to provide an unadulterated account of their experience, rather than tailor their story to specific individuals (e.g., a friend who has had a certain stance on the abortion issue). Similarly, anonymity allows for potentially muted or stigmatized groups to post information without fear of sanctioning. In a culture where abortion remains highly contested and talk about having had an abortion is often muted or stigmatized (Altshuler et al., 2017), it is likely that women may prefer to self-disclose their medication abortion experiences online rather than via face-to-face channels. Furthermore, because women traditionally constitute a co-culture who have historically been muted and must strategically use communication to participate in a dominant patriarchal society (M. Orbe, 2005; M. P. Orbe, 1998), scholars must study platforms where women are sharing unsolicited stories in back-channel outlets (e.g., online blogs).

Online blogs as a platform for unsolicited talk

One backchannel platform of unsolicited talk is online blogs. Blogs provide a computer-mediated platform where people can self-disclose their personal thoughts, feelings, and experiences to others online. The proliferation of blogs in the last decade has transformed the way that we, as a society, "share, create, and curate information with individuals and communities" (Becker & Freburg, 2014, p. 415). Blogs often resemble online personal journal entries that enable writers to freely express themselves in ways that may be less face-threatening or stigmatizing (M. Jones & Alony, 2008). One of the many applications and uses of blogs is to share experiences and events through storytelling.

Relational Dialectics Theory (RDT)

Because talking about one's abortion experience remains stigmatized and muted (Cockrill & Nack, 2013), examining women's stories after having had a medication abortion may illuminate the competing discourses surrounding this debated moral and social issue (e.g., largely evident in the two polarized movements: Right to Choice v. Right to Life), as well as some of the larger dominant discourses from the polarized political movements that influence how women tell their own medication abortion story. Given this goal, RDT (Baxter, 2011) is a relevant framework to assess the competing cultural norms and expectations, which are also referred to as discourses. At any given moment, discourses may be dominant/centripetal or marginalized/centrifugal (i.e., anything that deviates from the dominant discourse). Scholars use RDT as a framework to examine the interplay between certain discourses that then construct social meaning and reality for individuals. Within the theory, there are four types of utterances (i.e., speaking chains) from which dialectical tensions (i.e., centripetal vs. centrifugal) may stem: *distal already-spoken* – utterances reflecting the cultural meaning and discourses that cultural members give voice to in their talk; *proximal already-spoken* – utterances conveying past meanings and discourses within a given relationship; *proximal not-yet-spoken* – immediate response from the hearer in the interaction; and *distal not-yet-spoken* – anticipated responses of a generalized other within the culture. The purpose of this paper is to examine how, if at all, these four types of utterance chains are present within women's medication abortion narratives.

A second aspect of RDT (Baxter, 2011) is to understand how social reality is created discursively through power. Power is located in the struggle between marginalized/centrifugal and dominant/centripetal discourses. There are three ways that power can be located within discourses: diachronic separation, synchronic interplay, and discursive transformation. Diachronic separation occurs when discourses emerge in different texts or locations. Synchronic interplay is when discourses negate (total rejection of a competing discourse), counter (offer limited legitimacy to a discourse), and/or entertain (consider multiple worldviews/discourses or general ambivalence toward discourses) one another. Finally, discursive transformations occur when the interplay of competing discourses creates new meanings rather than remaining in opposition to one another (Baxter, 2011). This current study will focus on examining the synchronic interplay among the centripetal and centrifugal discourses.

A case study of women who have experienced medication abortion

To analyze women's personal narratives and the larger discourses influencing their talk about their own medication abortion, we conducted a case study of the website www.abortionschangesyou.com. We selected this website for several reasons: it is not openly politicized, bloggers do not interact with others, bloggers post anonymously, bloggers do not need to create an account in order to post, and the platform is a space for unsolicited stories with no reward or

compensation to those who post. Furthermore, from a strategic storytelling standpoint (Tyler, 2007), it is important to study women's blogs from an organization that recognizes and respects each woman's individual narrative, as opposed to propagating narratives that openly align with the agenda of only one political movement. The woman who created this website has had an abortion herself and openly shares this information on the "About Us" page. The naming of her own abortion experience grounds co-cultural theorizing (M. Orbe, 2005; M. P. Orbe, 1998) such that other women who feel muted may be empowered and capable of finding similar language strategies.

In this case study, we explore the complexity and consequentiality of women's language choices with anonymously telling their own medication abortion story, as well as offer the potential to capture the interplay of individual, organizational, and social discourses surrounding the abortion debate. The current divisiveness surrounding the socio-political climate in the U.S. about abortion provides further exigency and credence for this research. Our critical analysis is rooted in the interpretive paradigm with the purpose of explaining, describing, and illustrating the stories that women share on this website (Tracy, 2013). The following research questions guide our iterative analysis:

RQ1: What topics are women disclosing to the "generalized other" in their blog?

RQ2: What (if any) sites of struggle characterize women's abortion narrative?

Methods

We conducted a case study approach (Arden Ford et al., 2014) of one website, www.abortionchangesyou.com. Case studies are a contextual examination used to understand a phenomenon within a particular context "and with respect to multiple perspectives within that context" (Arden Ford et al., 2014, p. 118). By employing a case study approach, we were able to draw on multiple perspectives (e.g., 98 different blog stories) that were rooted in a specific context. This methodological choice is common in other communication research, where the unit of analysis is an organization and the goals are to provide an in-depth understanding of the unique particulars and complexities of the case within a larger social context (Norander & Brandhorst, 2017).

Our case study included 98 blogs from women who have had a medication abortion and shared their story on the website. We included all blogs posted between October 2007 – February 2018. This date range reflects the time period between the submission of the first medication abortion blog on the website in 2007, and the point at which we extracted our data for analysis in 2018. Women's blogs ranged in length from one paragraph to three pages of text, single-spaced (the average number of words for the 98 blogs was 655 words). All 98 blogs included content about one's own medication abortion; the vast majority (91 women; 93%) also discussed the events and emotions experienced before and after their medication abortion.

Data analysis and synthesis

The case study approach allows for different data analysis strategies (Norander & Brandhorst, 2017). Because the purpose of our case study is to develop a thick description of the case, using an interpretive analytic strategy is most prudent. We selected Baxter's (2011) contrapuntal analysis to study the meanings circulating around individual and relational identities evidenced within the language choices of the women blogging about their own medication abortion. Given the larger competing discourses about the legality of abortion in the U.S., we felt that the struggle of competing and contradictory discourses would likely be apparent in women's personal blogging narratives. Further, contrapuntal analysis (Baxter, 2011) offered a critical perspective to our analysis as we studied the voices of marginalized women (e.g., women who have had a medication abortion) whose perspectives are often muted and stigmatized in society.

To understand the competing discourses and how meaning was constructed through their interplay, we conducted the first stages of thematic analysis to identify the discourses evident within each blog post (Braun & Clarke, 2006). This process required the three coders to independently familiarize themselves with the entire data set: reading the blogs several times and conducting line-by-line coding that captured the essence of the story in each line. Many of the inductive analytic codes applied to the text were descriptive (e.g., uncertainty; not ready), process (e.g., discovering pregnancy, taking the pills), or in vivo codes (e.g., wanted baby; alone; Saldaña, 2013). The coders met regularly for five months to discuss the codes independently applied to each blog post. During this time, codes emerged into themes as processes were identified in the data and repetitively noticed by all three coders (e.g., changing self perception, silence, responsibility, good parenting). Discrepancies in coding were discussed during coding meetings and resolved through group consensus (Strauss & Corbin, 1990).

During the third and fourth months of data analysis, we went back to the data set to identify where discourses competed (e.g., culpability; justification). Here, we paid particular attention to where the bloggers used instances of negating (e.g., claiming another discourse as irrelevant or rejecting it), countering (e.g., offering a particular discursive position in replacement of another), and entertaining (e.g., not completely rejecting a discourse, but instead noting the potential possibilities with different discourses; Baxter, 2011). Women used negating when saying, "can't," "not," "couldn't," and "never." Examples of countering were most apparent when women used the word "but." Entertaining often occurred when women used the words "possibility" and "could have." Finally, we identified where and how competing discourses interpenetrated (Baxter, 2011). Dialogically contractive discursive practices are silenced discourses. Examples of these discursive practices included negating talk, such as: "can't talk about the abortion," or "there was no other choice." In contrast, dialogically expansive discursive practices are discourses that are encouraged and amplified. Women used these discourses when saying things like: "I don't want the procedure, but I don't want the baby" or "hoping for a brighter future now that it is over."

Data were analyzed until the point of theoretical saturation (i.e., no new thematic categories were present in the blog posts; Strauss & Corbin, 1990), which occurred after the 54th blog post. However, we continued to analyze the remaining blog posts in an effort to verify that our analysis of the discourses evident in the 54 posts accurately reflected all of the posts within the entire data set. Further, we wanted to extract the best exemplars from the entire case study and desired that quotations within all posts be considered for representation. Clear and concise exemplars of competing discourses within women's narratives were then selected and agreed upon by all coders.

Trustworthiness and rigor

Evaluation of the quality of case study research should be determined by criteria associated within the naturalistic paradigm (Arden Ford et al., 2014). Trustworthiness is the criterion that assesses the credibility, transferability, dependability, and confirmability of the data collection and analysis processes (Lincoln & Guba, 1985). We upheld these principles when conducting this study by beginning with a careful design that clearly defined its purpose, research questions, and notion of "boundedness" (i.e., establishing the limits and context of the case; Arden Ford et al., 2014). Second, we spent sufficient time developing and analyzing the case: our analysis transpired over five months. Third, we upheld the principles of reflexivity by using inductive coding for all blog posts and writing individual and group memos throughout the entire coding process as a way to remain transparent and keep a data audit. Fourth, we had a team of three female coders, which allowed for the presence of multiple feminine perspectives.

Findings

Our research questions focused on the topics that women discussed in their personal online blogging narrative posted to www.abortionchangesyou.com (RQ1), and what (if any) sites of struggle were evident in these narratives (RQ2). Our contrapuntal analysis (Baxter, 2011) rendered four sites of dialectical tension: *only choice vs. other alternatives*, *unprepared vs. knowledgeable*, *relief vs. regret*, and *silence vs. openness*. Each site of struggle characterized a different noteworthy moment within a woman's medication abortion experience: the decision, the medication abortion process, identity after the abortion, and managing the stigmatizing silence before and after the abortion. When recounting their decision to have an abortion, women referenced the struggle of *only choice vs. other alternatives*. As women discussed the medication abortion process, the competing discourse of *unprepared vs. knowledgeable* was evidenced. Women's narratives about their identity after the abortion indicated the dialectical struggle of *relief vs. regret*. Finally, the challenges with managing the tension between *silence vs. openness* pervaded women's narratives. Below we discuss each site of struggle using exemplar quotes from women's blogs. Quotes were not edited from their original post.

The decision: Only choice vs. other alternatives

Part of women's narratives included a detailed account of their decision to have a medication abortion. This decision was described as being rife with contradiction, and not a flippant choice. Women enumerated various reasons that were influential in their decision-making process: bad timing, financial instability, relationship problems, lack of family support, not married, too young, too many other children, not prepared to be a parent yet, and/or best decision given the circumstances. After stating one of the aforementioned reasons, 92 women (94%) also explained that abortion was the only or best option given the circumstances. For example, one woman said: "I felt the child growing inside of me. I was rubbing my stomach without me even knowing. I felt the doubt in my heart, but kept telling myself this is the best decision I needed to make" (6-18-17). A different woman recounted:

"I always leaned more towards keeping the baby and my boyfriend more towards abortion. I knew I could have the baby but it would be difficult. We both work jobs that barely pay over minimum wage and we both were scared to grow up and care for a child" (10-24-17).

Collectively, these exemplars illustrate how any possibility of keeping the baby was negated by one of the reasons that warranted the need for having a medication abortion. Many of the reasons women cited for choosing abortion align with the discourses from the Right to Choice movement: "A pregnancy to a woman is perhaps one of the most determinative aspects of her life. It disrupts her body. It disrupts her education. It disrupts her employment. And it often disrupts her entire family life" (*Roe v. Wade*).

However, the decision to have a medication abortion was not always independently made by the woman. In fact, 52 women (53%) reported that the father to their child or other family members (e.g., parents) negated women's own desires to keep the baby. For example, one woman said:

"I remember my husband telling me, 'well, don't expect me to be too happy with the idea of having it if you decide to keep it. I won't be too loving.' That was a knife through my heart and I made the tough decision to go through with the abortion" (7-6-12).

Other family members also influenced women's medication abortion decision, albeit her own desires to keep her baby:

"But my father on the other hand was a different story. He is an old school Puerto Rican who told me that I had to leave if I kept the baby. I had 2 weeks to get an abortion or else he would disown me forever" (3-8-2018).

In both accounts, women communicated their personal choice to have their baby; yet, their choice was negated by family and friends who advocated that abortion was necessary. Centrifugal discourses about others influencing or pressuring women to have an abortion are marginalized discourses.

Finally, when making their decision, 48 women (49%) reported vacillating between keeping their baby and having a medication abortion. Ultimately, outside circumstances or other people influenced their decision to abort. As mentioned earlier, 92 women (94%) shared that abortion was the best or

only option available given the circumstances. In many of these narratives, women did not believe nor realize that other alternatives, besides abortion, were tenable options until after having the abortion. For instance, one woman said:

“They all tell you ‘it’s your choice’ in the moment, but you don’t feel that it is. Being unable to afford it, unable to tell your loved ones, not having the help or feeling unable to support a child. When your partner doesn’t want it like you do. All these things push you, blind you to a decision that you don’t realize will destroy you” (8-23-17).

Similarly, another woman recounted: “I was kind of excited but I was so scared to tell my family I told my mom and her first response was I hope you’re getting an abortion. You’re going to be a terrible mom” (11-5-17). Both exemplars illustrate the distal and proximal already-spoken discourses that influenced each woman’s decision to have a medication abortion. Ultimately, these centripetal discourses (coming from society, the pro-choice movement, other people in their lives, or their own fears) negated the centrifugal discourse that other alternatives (adoption or keeping their baby) were justifiable options available to them.

The medication abortion process: Unprepared vs. knowledgeable

Medication abortions where women undergo most of the process individually at home with limited assistance from a medical provider are becoming more commonplace (Biggs et al., 2019; H. E. Jones et al., 2017). While this process is generally reported to be safe and adhere to evidence-based guidelines (H. E. Jones et al., 2017), little is known about women’s personal experiences with having this type of abortion. All women in this case study reported having had a medication abortion. Forty-eight women (49%) provided detailed accounts of their actual medication abortion experience at home. Women said things like: “I felt her come out” (1-8-16). Some women detailed the hardships of this process by saying: “I was in so much pain on the bathroom floor” (3-15-18); “the pills made me vomit, lose control of my bowels, sweat, faint, pass out, and go into full labor” (10-9-09); and “I lay on my bed in the fetal position, holding my stomach” (9-5-15). Other women did not self-report such negative experiences: “The actual process of taking the pill was frightening but not as bad as I imagined” (9-8-15) and “I just popped some pills and got a period” (7-1-15).

In analyzing women’s talk about the medication abortion process, a second site of struggle was identified: *knowledgeable vs. unprepared*. In this struggle, women discussed how they were told certain information about the medication abortion process (e.g., when to take the pills, what the pills do, the need to contact a provider if complications arise), but ultimately this information was insufficient, limited, or misleading. Fourteen women (14%) reported being inadequately prepared about what to expect during the medication abortion process. For example, one woman said:

“They lied to me and said they would give me some pills that would make it just like a late period with a little cramping ... The pain of the contractions was so intense I felt like my intestines

were pulled out slowly. I collapsed screaming on my bathroom floor, sweat, tears, blood, vomit, and shit all over me” (10-9-09).

Similarly, a different woman recounted:

“They told me, if you by chance are in pain you can take these pain relievers. If by chance I’m in pain? That sounded like the process would be easy and not so painful. Well NO that was not the case, within 30 minutes I felt really bad cramping. It just kept getting worse and worse. I was crying and moaning from the pain. I literally thought I was dying” (9-2-17).

In both instances, women’s personal abortion experiences did not align with the proximal-already-spoken messages (e.g., “it’s just a pill”) that they were told by their medical providers.

When women’s personal experiences contradicted what they were originally told by health care providers, family, or friends women felt deceived. One woman communicated her frustration by saying: “They told me it wouldn’t hurt and I wouldn’t feel a thing. THAT WAS SUCH A LIE. I felt everything, I heard everything, I seen everything. I ended up blacking out from the pain and puking all over myself” (11-5-17). Similarly, another woman said:

“We were told we would go back to normal and it won’t affect us but they were wrong!!! All I feel is emptiness and hatred. I used to be the happiest most positive girl. All I want is to take it back” (12-15-14).

Even if women did not explicitly report feeling deceived, many women stated that they were inadequately prepared about what to expect. For instance, one woman said: “I knew to expect blood clotting, but nothing could’ve prepared me for seeing her body. It was the color of my own skin, and was actually starting to look like a person” (1-8-16). Within women’s narratives, they expressed a desire for more detailed information about things such as: potential side effects, the intensity of cramping and bleeding, what to do after passing the baby, and potential negative emotions (e.g., fear, uncertainty, sadness, pain) felt after the abortion. When this comprehensive information was not communicated to them prior to taking the pills at home, women reported feeling misled, misinformed, and even deceived. These types of experiences and feelings after having had a medication abortion remain centrifugal discourses that are muted within the abortion debate.

Identity after medication abortion: Relief vs. regret

A third site of dialectical struggle was found in women’s talk about their identity after the medication abortion. Most women (N = 81; 83%) reported that their medication abortion changed them, which is not surprising given the name of the website: *Abortion Changes You*. Of noteworthy significance is understanding *how* women talked about these changes and the tension evident in this part of their narrative. Of the 81 women (83%) who stated feeling *changed* after their medication abortion, 75 women (77%) reported being changed in a negative way. Here, women said things like: “I really thought that I could somehow go back to the way things were before finding out I was pregnant. But I cannot. I am not the same person, and my husband is certainly not the same either” (7-11-11). Negative changes often occurred when women’s

actual abortion experience did not align with their preconceived ideas about what to expect. These ideas were informed by larger discourses from society, as well as messages from others (e.g., health care providers). Three women indicated a positive change after their abortion by noting something like:

“Abortion did change my life ... As soon as the stomach cramps (only slightly worse than regular menstrual pains) went away, I felt like a whole new person. I couldn’t believe how much energy I had again. It was like waking out of a deep depression” (7-1-15).

Positive changes were denoted by experiencing an initial sense of relief with no longer being pregnant. Finally, three women were ambivalent or didn’t report their change as positive or negative. One woman said: “I truly believe there is no right and wrong with this situation, it is a life changer but it’s your choice” (9-7-10).

Women discussed various issues when talking about change: impact on their emotional health as a result of the abortion, differences in their relationship with their partner/spouse, and new perspectives on their general views of abortion. However, conflicting emotions were evident across all women’s blog posts. For instance, one woman said:

“I went home and confessed to my mother ... She helped pull the gigantic blood clots from my body ... No one told me it would be like this; the clinic simply gave me what I asked for without telling me what it entailed” (7-20-16).

Similarly, another woman recounted: “I thought maybe after the due date I would feel better, but it doesn’t end there. It NEVER ends! The pain and emptiness stays there forever” (4-30-17). In these different accounts, the women alluded to their initial expectations of what the medication abortion would entail or what others told them would happen after their abortion. When a woman’s actual medication abortion experience did not align with these messages, women felt disempowered, vulnerable, lost, upset, and sometimes deceived.

When discussing the changes experienced after the abortion, many women talked about emotional changes. One woman said:

“At first it all seemed like a weight had been lifted and everything was okay then I started to feel really sad and low and now all I do is think about how many weeks pregnant I would have been and what my baby would look like and I miss so much” (4-26-10).

As mentioned, processing one’s abortion experience was emotional and took time. Some women wrestled with experiencing negative and difficult emotions after having their abortion. In fact, 37 women (38%) explicitly stated problems with anxiety, depression, drug abuse, and suicidal thoughts as a result of the abortion. For example, one woman said: “I am haunted by the image of my tiny baby. I always will be. I cut myself and even wanted to die” (3-22-13). Another woman recounted: “Looking at my kids thinking of another beautiful child. Couldn’t live with myself. Wishing God would take my life” (12-16-11). Collectively, these exemplars illustrate women’s emotional changes about processing of their medication abortion.

Finally, 75 women (77%) explicitly stated that they regretted their decision to have an abortion. However, the

term regret was rife with contradiction and also included talk about initial relief. For instance, one woman said: “I know I did the right thing for myself and it would be a lot harder for me right now. But I still would give anything to go back in time and keep my baby” (11-19-12). Regret was regarded as a process that was realized over time and through one’s life experience. One woman stated: “Had I known how badly I would feel now, I would have kept the baby, even if I had to go through it alone” (10-21-15). Another woman elaborated upon this process by saying:

“Knowing what I know now at almost a year later I would not have the abortion. That was my child and I should have done what I needed to do to give them a great life. I thought I had no options but I did. I should have put my child first. No matter how early the abortion is its still a growing life and i wish i had done things differently” (4-30-17).

In both accounts, women defined regret as the emotional pain, suffering, remorse, and guilt felt after the medication abortion. Yet, these emotions were often coupled with initial feelings of relief from no longer being pregnant. In sum, the decision to have a medication abortion was significant, transformative, and lifechanging for these women. One woman noted this change by saying: “From the outside, our life looks exactly the same as it would have. But on the inside, everything has changed for me” (10-21-15). Collectively, these accounts expose how the different emotional changes resulted in a lived, dialectical tension between their life before the abortion and their life after the abortion.

Managing the comprehensive stigmatizing silence: Silence vs. openness

Across women’s narratives, there existed an overarching dialectical tension of *silence* vs. *openness*, which was difficult for many women to manage when interacting with others. In this struggle, women shared how their medication abortion was often a solo, private experience that was not openly shared with others. Many women decided *not* to inform certain family members about their pregnancy and abortion. Women noted feelings of shame, embarrassment, worry, or fear as some of the reasons for not telling others. Along with stating these emotions, women said things like: “I never told the father and I don’t intend to” (8-4-17); “I don’t know if I will ever tell my husband and children about what I did” (2-11-12); or “I couldn’t talk to my family” (3-16-17). The initial decision to remain silent made it difficult to talk openly with others about their feelings and experiences after their medication abortion. Silence was also experienced in other ways: one woman was glad she was home alone during her abortion so no one could hear her, while a different woman left the abortion clinic and began crying and said, “why is there so much silence here?” as she was taking her pill alone in her bathroom at home.

Even if women did allow certain family members to become privy to their abortion decision, openly discussing their feelings after the abortion remained difficult. When talking with others, one woman said: “I love my husband but it is beyond difficult for me to talk to him about this,

because I know he wants nothing more than to just move on from this” (4–28–18). A different woman recounted: “My close friends know here but I don’t really feel I can talk to them about it. I don’t feel like i can talk to anyone about it” (2–9–13). Despite these women’s desires to talk about their abortion, others (e.g., the baby’s father, their husband, family members) refused to engage in conversation with them. As a result, women said things like: “I feel like I have no one to speak to about it since he doesn’t think about it the way I do” (9–8–15), and “I try to talk about it with my family and the baby’s dad but they all tell me it’s in the past” (10–28–17).

Oftentimes, certain dates (such as their child’s due date) or friends with other babies who are of similar age to their “would-have-been child” led to triggering events where women desired to express their feelings with others, but felt like they couldn’t talk openly. For instance, one woman said: “But I haven’t really been able to share the true regret and near constant jealousy of my loved ones engagements or pregnancies” (11–21–16). Another woman stated: “I knew I had to have an abortion, but these feelings I have right now I never imagined I’d have. I don’t want to go out, I don’t want to tell anyone, all I feel like doing is crying” (7–8–18). Thus, the isolation and silence leading up to her own medication abortion continued to pervade after the abortion, creating additional communication challenges with freely expressing her emotions with family and friends.

Silence was often described as being frustrating and challenging. In fact, 59 women (60%) reported feelings of isolation and alienation. As a result, some women personally attacked themselves. For example, one woman said: “I feel like I’m living a lie I get up get ready for work get my family up like normal the days go on like normal but I’m not normal I killed my baby I’m a monster!!” (3–14–17). Similarly, a different woman wrote: “As a mom I feel like a monster and I have to act like nothing happened” (4–18–17). These demeaning language choices (e.g., monster, killer) are present in the distal-already-spoken societal discourses about abortion. Women’s awareness of these larger discourses led some women to write about their intentional use of selective language choices when talking about their abortion with others. One woman shared: “I tried to find an OBGYN that could see me ASAP. I went in and told them I had a miscarriage because I was ashamed of the truth of what I did” (3–21–18). Finally, some women reported struggling in silence by saying things like: “I am in desperate need of assistance and I am too embarrassed to attend an in person support group” (11–21–16), and “And when I got home, I had to hold it all in. I was so ashamed of my choice. I couldn’t let anyone know” (2–11–11). Even though these women were able to anonymously write about their abortion on this website, they felt muted by their loved ones because of the centripetal discourses of shame and embarrassment associated with abortion.

Discussion

A national study that assessed women’s support for and interest in alternative models of abortion provision found that about half of

U.S. women are supportive of and nearly one-third are interested in medication abortion (Biggs et al., 2019). The growing interest and practice in this type of abortion provision warrant scholars to understand women’s experiences. Our study is the first in the U.S. to conduct a case analysis of women’s online blogging narratives about having had a medication abortion. We focused on understanding the discursive dynamics and contradictions that influenced and shaped women’s talk about their own experiences. Our analysis rendered four sites of dialectical tension: *only choice* vs. *other alternatives*, *unprepared* vs. *knowledgeable*, *relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different stage of women’s medication abortion narrative: the decision, the medication abortion process, after-abortion identity, and the general stigmatizing silence associated with abortion.

As other scholars have noted (Kimport & Doty, 2019), we found that women relied upon language choices that aligned with the existing ideological frameworks from both the Right to Life and Right to Choice movements. For instance, some women used the words “fetal tissue,” while other women used the word “baby” when referencing their pregnancy. Women also explicitly mentioned distal already-spoken messages from both movements about how they were told “it’s just a pill” or “I’ve killed my baby.” Such language choices are not idle linguistic distinctions, but rather indicate a woman’s awareness of the different semantics and terminology surrounding the larger cultural narratives about abortion. This awareness was particularly evident when women discussed the overarching silence stigmatizing one’s abilities to openly talk with family and friends about their medication abortion experience. Thus, women’s talk about their own personal experiences, their justification for having an abortion, and their own sense-making after the medication abortion were shaped by the available heuristics and frames from larger cultural discourses and political movements (Kimport & Doty, 2019).

Cultural narratives of abortion are powerful and construct meaning and truth (Ludlow, 2008). While a woman’s personal story about her medication abortion is individual and now occurs in a more private setting (e.g., at home), this experience remains social and political, defined, and reified by larger cultural narratives and semantics (Beynon-Jones, 2017; Cockrill & Nack, 2013). The sexual liberalism script that reflects positive attitudes toward nontraditional sexual behaviors influences individual’s attitudes about abortion (Tokunaga et al., 2015), as well as their own narratives about medication abortion. We found evidence of these larger discourses within women’s talk about their own medication abortion, and in particular, their rationale for their decision, their description of the medication abortion process, their reflections on their identity after the abortion, and the overall stigmatizing silence resulting in a muted voice and the public illegitimacy of their own narrative. For instance, many of the justifiable reasons recounted by women in this case study for having an abortion align with the centripetal discourses of the Right to Choice movement regarding bodily rights and a woman’s freedom of choice. Among women having abortions in the U.S., finances and lack of readiness are the most commonly cited reasons for choosing abortion (Finer et al., 2005).

The presence of larger cultural narratives can result in dialectical tensions as one seeks to construct her own abortion narrative and considers disclosing that narrative to others. In

particular, many women described experiencing both relief and regret after their abortion. Historically, these two emotions have been juxtaposed and positioned as binary emotions that are socially and politically aligned (Ehrlich & Doan, 2019). The Right to Choice movement discourse aligns with the notion that abortion proffers emotional relief, whereas the Right to Life movement discourse positions itself with abortion resulting in regret. This polarized alignment and framing results in both movements speaking different languages and never fully listening nor engaging with the other (Wiederhold, 2014). One proposed origin of this framing dates back to the legal reasoning of the 2007 U.S. Supreme Court case *Gonzales v. Carhart*, where the federal partial-birth abortion ban was upheld. However, our analysis of women's narratives post-medication abortion exposes the complex duality of these two emotions often being experienced in tandem, as opposed to being simplistic binaries. The either-or, unidimensional script from both the Right to Choice and Right to Life movements – abortion provides either relief or results in regret – fueled a sense of tension for many of the women as they processed their identity after the abortion and considered openly disclosing those private experiences with others. Thus, these women's narratives illustrate that one's individual experiences with having had a medication abortion may result in a both/and: initial relief coupled with later regret. A reliance upon political movement discourses to construct one's own narrative may continue to marginalize or invalidate one's own private medication abortion experience when the larger scripts remain politically charged and polarized (LaRoche & Foster, 2018).

The stigma and risk that characterize the topic of abortion are influenced and shaped by the larger centrifugal discourses from both the Right to Choice and Right to Life movements (Beynon-Jones, 2017; Cockrill & Nack, 2013). For example, Cockrill and Nack (2013) found that women seeking an abortion often attempt to manage the stigma of abortion through non-disclosure, stating their reasons for having an abortion as "exceptional" and necessary, or condemning the Right to Life perspectives about abortion. In a different study on Southside Chicago African-American adolescent females, the majority of sexually active teens never talked with their parents about the topic of abortion, and almost 20% expressed fears of harm or eviction if their parent were to learn of an abortion in their past (Sisco et al., 2014). In our case study, we found that women also experienced stigma, silence, and fear that led them to remain private and/or secretive with certain individuals throughout their medication abortion experience. Silence before or during the medication abortion process resulted in women experiencing additional challenges later on with talking openly about one's experiences. Altogether, these findings align with communication scholars who have found that when private health information disclosures are deemed as being threatening or stigmatizing, one's private health information remains concealed (Baxter & Akkoor, 2011; Ebersole & Hernandez, 2016). This is important because secrecy of one's abortion is associated with poorer coping (Major & Gramzow, 1999; Major et al., 1997), and may result in further isolation and lack of social support from others (Cockrill & Biggs, 2017).

Recent movements such as Shout Your Abortion and #YouKnowMe have tried to dispel the stigma and silence surrounding abortion. However, these movements remain politically aligned and purport the "American Dream" abortion narrative: I was able to go to college/graduate/get a good job due to my abortion. These more recent public narratives frame abortion as a restitution or quest experience (Frank, 1995), where women are portrayed as being able to return to normalcy and good health, or regard their abortion story as one part of their personal journey that they were able to overcome. While such discourses were evident in some women's blogs and have been shown to reduce abortion stigma when openly disclosed (Cockrill & Biggs, 2017), many women's narratives within this case study characterized chaos narratives (Frank, 1995) where the abortion experience interrupted their daily lives and left them feeling out of control. Most notably, over 50% of the sample reported that the father to their child or other family members used negating language as a means to justify a woman's need for an abortion, albeit her own desires to keep her baby. In addition, 75 women (77%) regretted their decision, and 37 women (38%) reported struggling with mental illness and suicidal thoughts after the abortion. While previous scholarship has also found evidence of some women experiencing negative outcomes after an abortion due to a lack of decision-making power and limited social support (Kimport et al., 2011), as well as possible significant relationships between abortion and mental health problems (see Fergusson et al., 2013; Reardon, 2018), these centrifugal discourses remain muted and marginalized in the U.S. abortion debate.

Limitations and directions for future research

As with all scholarship there are limitations. Most notably, there is a lack of generalizability due to the limited scope: we only analyzed women's medication abortion narratives anonymously posted to one website. However, it is important to note that the purpose of this project was to make analytic generalizations based on gathering an in-depth descriptive understanding of these women's medication abortion narratives. Second, all qualitative case studies are limited by the sensitivity and integrity of the investigators. We attempted to surmount this obstacle by having three qualitatively trained female researchers who completed independent coding and collectively participated in the contrapuntal analysis process. Third, case study research is criticized for not having a clear set of systematic procedures (Yin, 2014). To address this concern, we sought to clarify and provide transparency with the methodological techniques used. Fourth, the anonymity of women's blog submissions to the website did not allow us to gather and report the social demographics of the women who anonymously shared their abortion narratives, which again hinders the generalizability of our findings. Finally, the population of women who write an anonymous post about their abortion experience may be different from those who do not.

All of these limitations provide avenues for future research. Most importantly, this single case study demonstrates the need for a broader, pluralistic, mixed-method research strategy that

assesses women's medication abortion narratives, particularly given its increased popularity amongst women seeking this type of abortion provision. Such research could interview women who have had a medication abortion, as well as use surveys to assess different variables such as demographic factors, health literacy, and privacy management strategies employed when talking about one's medication abortion.

Conclusion

In sum, our findings show that the medication abortion experience is rife with tension and contradiction. This complexity and duality are not evident in much of the larger cultural discourses and political debates about abortion. Many women in this case study noted that their decision to have a medication abortion was not a flippant decision or an easy choice where women remained unscathed. Women's narratives about their medication abortion experience were complex, and no singular narrative fully encapsulated or defined what women experienced during and after their medication abortion. Therefore, it is critical to transcend the silence in order to expose both sides of the debate and understand how these larger discourses influenced women's personal language choices when constructing their own abortion narrative and anonymously sharing it with others online. The tensions and dialectical struggles experienced after having a medication abortion and attempting to share it with others remain silent from public discourse and debate (Hallgarten, 2018). Presently, this silence positions one's abortion story as an either-or, binary experience that is politically aligned with one movement or another. The larger discourses prevalent within both the Right to Life and Right to Choice movements impact the liminality of women who are contemplating a medication abortion and affect their own narrative reconstruction and sense-making after their private medication abortion.

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EXHIBIT 14

Covert network provides pills for thousands of abortions in U.S. post Roe - The Washington Post

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Covert network provides pills for thousands of abortions in U.S. post Roe

Amid legal and medical risks, a growing army of activists is funneling pills from Mexico into states that have banned abortion

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By [Caroline Kitchener](#)

October 18, 2022 at 6:00 a.m. EDT

Monica had never used Reddit before. But sitting at her desk one afternoon in July — at least 10 weeks into an unwanted pregnancy in a state that had banned abortion — she didn't know where else to turn.

"I need advice I am not prepared to have a child," the 25-year-old wrote from her office, once everyone else had left for the day. She titled her post, "PLEASE HELP!!!!!!!!!"

Within hours, she got a private message from an anonymous Reddit user. If Monica sent her address, the person promised, they would mail abortion pills "asap for free."

Monica didn't know it at the time, but her Reddit post connected her to a new facet of the battle for abortion access: the rise of a covert, international network delivering tens of thousands of abortion pills in the wake of the Supreme Court ruling in June that struck down *Roe v. Wade*.

The emerging network — fueled by the widespread availability of medication abortion — has made the illegal abortions of today simpler and safer than those of the pre-*Roe* era, remembered for its back alleys and coat hangers. Distinct from services that sell pills to patients on the internet, a growing army of community-based distributors is reaching pregnant women through word of mouth or social media to supply pills for free — though typically without the safeguards of medical oversight.

"You're truly [an] angel," Monica wrote in a string of messages reviewed by The Washington Post. "I think tonight will be the first night I will actually be able to sleep."

This account of the illegal abortion movement that has grown quickly since the Supreme Court ruling is based on interviews with 16 people with firsthand knowledge of the operation, and includes on-the-ground reporting in four U.S. cities and Mexico. Many who spoke to The Post did so on the condition of anonymity to discuss activity that potentially breaks multiple laws, such as practicing medicine without a license and providing abortions in states where the procedure is banned. The Post was permitted to observe distributors handling pills in antiabortion states on the added condition that their locations not be identified.

Those interviewed described a pipeline that typically begins in Mexico, where activist suppliers funded largely by private donors secure pills for free as in-kind donations or from international pharmacies for as little as \$1.50 a dose. U.S. volunteers then receive the pills through the mail — often relying on legal experts to help minimize their risk — before distributing them to pregnant women in need.

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The system could upend Republican plans for a post-*Roe* America. Despite the strict abortion bans that have taken effect in over a dozen states, some antiabortion leaders fear that the flow of abortion pills could help make abortion more accessible than it was before *Roe* fell. Las Libres, one of several Mexican groups at the center of the network, says its organization alone is on track to help terminate approximately 20,000 pregnancies this year in the United States. That amounts to about 20 percent of all legal abortions that took place in 2019 in the 13 states where abortion is now almost entirely banned.

“Soon there will come a moment when we won’t be able to count any of this,” said Verónica Cruz Sánchez, the director of Las Libres, adding that the group works with a U.S.-based volunteer network that numbers about 250 and is “growing, growing, growing.”

The leader of another Mexico-based group that supplies pills, Red Necesito Abortar, said the elaborate volunteer structure was “like a spiderweb.”

“Once we get the pills into the U.S., they can distribute them across the whole country,” said Sandra Cardona Alanís, the group’s co-founder.

Most people interviewed for this story acknowledged that the network they are building is far from ideal, with participants taking legal and medical risks they would not face if abortion was still permitted nationwide.

The medication — a two-step regimen of mifepristone and misoprostol — was approved by the U.S. Food and Drug Administration in 2000 with a prescription, for use during the first seven weeks of pregnancy, a limit that was then extended to 10 weeks in 2016. But people involved in the network described a process that goes beyond what the FDA has endorsed. Organizations like Las Libres offer abortion pills without a prescription and, typically, without access to a medical professional — occasionally providing medication to those who say they’re at or beyond the FDA’s 10-week limit. To avoid detection in antiabortion states, the group also mails pills unmarked and unsealed, often in old bottles used previously for other medicines.

Some experts worry that as demand soars and cross-border networks expand to include less credible suppliers, women could start to receive illegitimate pills that are ineffective or, worse, dangerous. Fake abortion pills have been circulating in other countries with strict antiabortion laws, said Guillermo Ortiz, an OB/GYN and senior medical adviser with Ipas, an international abortion rights nonprofit.

“It’s scary,” he said. If women don’t know how to recognize real abortion pills, “it could cause huge harm.”

Other experts are less skeptical. Kristyn Brandi, a doctor and spokesperson for the American College of Obstetricians and Gynecologists, the leading professional organization for OB/GYNs, said she feels confident that patients can carry out abortions safely without medical supervision — as long as the pills they receive are clearly labeled.

“Medication abortion is one of the safest processes that you can go through,” she said. “Regardless of where you get that medication, based on the science ... what’s happening in your body shouldn’t be any different.”

Monica’s abortion pills arrived in the mail on a Friday afternoon, hidden inside a cat flea medication box. While the pills themselves were sealed and labeled, Monica’s boyfriend said he wasn’t sure if she should take them.

“What if they’re fake?” he recalled asking. He’d recently read news reports of other drugs that had been laced with fentanyl.

“What if they’re sending you something that isn’t even the abortion pill?”

By that point, Monica — who relayed her experience to The Post in real-time texts and calls, and then later in a lengthy interview at her home — had known about her pregnancy for over a month. She knew she wanted to have kids one day, but she and her boyfriend lived paycheck to paycheck, without health insurance. At the end of the month, they’d sometimes get down to their last \$40 — and have to decide between groceries and gas.

“I’m scared, too,” she said she told her boyfriend.

“But this is my only option.”

A nurse joins the network

Two weeks earlier, on the day *Roe* fell, a nurse in a different city rushed from room to room at the abortion clinic where she worked — frantically telling patients where they could order illegal pills now that their state had banned abortion.

“Do you have Insta?” she asked at least 20 patients that day, waiting as they pulled up their Instagram accounts.

She instructed each patient to follow an online resource called Plan C, which compiles a list of sources where patients can buy abortion pills on the internet. The nurse reviewed various options, including Aid Access, the prominent online service run by Dutch physician Rebecca Gomperts, as well as various online pharmacies that sell abortion pills illegally to people in antiabortion states.

The next day, one of those patients found the nurse in the grocery store.

“I have the money,” the woman said, her eyes desperate. “Will you buy the pills for me?”

The nurse couldn’t remember the patient’s name, but she remembered other details the woman had shared about her life — pleading in Spanish in the clinic hallway five hours after the Supreme Court overturned *Roe*. A mother of four, the woman was an undocumented immigrant from Mexico with a history of severe pregnancy complications and a Catholic husband who did not believe in abortion.

She couldn’t order the pills herself, she explained, because she didn’t speak English and had no reliable access to the internet. If the pills came to her home, she also worried her husband would find them.

Hyper-aware of the other grocery carts moving around her, the nurse considered all she might lose if she helped the woman and got caught. Where she lived — a Republican-led state in the South — she knew she could be stripped of her nursing license for distributing abortion pills. Maybe even go to jail.

The nurse promised herself she would do it just this once.

“I’ll tell you when I have them,” she said to the woman.

Securing the pills was easier than the nurse ever imagined: She called a friend, who sent her the number for Las Libres. The organization, she learned, had been working with many volunteers like her — helping patients who, for one reason or another, couldn’t buy pills on their own.

Many patients had never heard of Plan C or Aid Access. Some couldn’t afford the advertised price tag of \$100 or more. Then there were patients like the woman in the grocery store, desperate for pills but without a safe place to receive them.

On the phone with Las Libres, the nurse had requested just one set of abortion pills — enough to help her former patient. But, she said, the package arrived three days later with the means to end five pregnancies.

Las Libres soon followed up with the address for a woman in a different city.

The nurse, in her late 20s, thought about the lawmakers who had ushered in these laws — and those who had implemented similar restrictions years ago in Mexico, where she'd had to secure her own illegal abortion at age 16. She still remembered her feet in the stirrups in an empty apartment building. The unsure medical student who performed the abortion. The speculum and dilator boiling in a pot of water on the stove.

"I want those politicians to feel powerless," the nurse said of her decision to join the ranks of the illegal abortion movement. "I want them to feel the same way my patients feel."

She mailed her second set of pills the next day.

A supplier secures the pills

Before the pills arrived in the nurse's mailbox, they occupied a corner of Cruz Sánchez's closet — tucked away in the central Mexico headquarters that has housed Las Libres for almost two decades.

The pill supplier and her team of seven employees work from a mountainside home in Guanajuato, hidden from the road by an eight-foot electric gate and a tangle of red trumpet vines. Inside, the Las Libres office hums with the rhythms of a family: Cruz Sánchez's nephew brews a pot of coffee while her sister fries up leftover chilaquiles, chatting about everybody's weekend plans before they all have to get to work.

When Cruz Sánchez, 51, started Las Libres in 2000, she envisioned a feminist activist organization that would help Mexican women in desperate situations. In its early years, the group provided legal counsel for victims of domestic violence and demanded freedom for women whose abortions had landed them in jail. They've long provided free abortion pills without facing any legal trouble, despite recent laws in Mexico that criminalized abortion.

It wasn't until Texas banned most abortions in the fall of 2021 — one week before Mexico's Supreme Court decriminalized the practice across that country — that Las Libres began to consider an international expansion. Suddenly, Cruz Sánchez was getting calls from women across the border, begging for pills.

"We wanted to help the women in Texas because we understood their situation," Cruz Sánchez said. "We'd experienced it."

Demand skyrocketed as soon as *Roe* was overturned in June, Cruz Sánchez said. Las Libres went from sending 10 sets of pills to the U.S. every day to sending over 100 — all at no cost to the patient.

The rapid expansion has only been possible, Cruz Sánchez said, with the help of U.S. volunteers who find some of the patients and shepherd the pills along to their final destinations. Since the Supreme Court decision, she said, she has been inundated with messages from Americans eager to take a stand against the ruling. In one state, she says, she is working with a group of registered nurses. Elsewhere, 50 pastors and priests.

Some of the volunteers work with U.S.-based abortion funds and other abortion rights groups, connecting with pregnant patients through established pipelines that existed long before *Roe* fell. Others are doing this work for the first time, Cruz Sánchez said.

"They just show up and say 'I want to organize my community, my neighbors, my friends — and I'm going to make a network,'" she said.

These days, the women of Las Libres spend much of their time fielding calls and texts from Americans, hunched over laptops at a table strewn with sticky notes and boxes of mifepristone. Cruz Sánchez regularly logs five or six Zoom calls a day — fundraising with American donors, or teaching volunteers how to safely join her efforts.

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Until recently, Cruz Sánchez said, Las Libres received all its pills as in-kind donations. International advocacy organizations mail large shipments of pills to their office, she said. Individuals come by with donations of misoprostol, widely available at Mexican pharmacies to treat stomach ulcers. Sometimes Mexican pill distribution companies send over a batch of pills that is about to expire, free of charge, Cruz Sánchez said.

When American demand started outpacing the stash in her closet, Cruz Sánchez said, she called her contacts around the world, searching for the cheapest supplier. Las Libres had roughly \$15,000 to spend, she said, from mostly American donors — the product of fundraising efforts they'd stepped up since June. On one recent Zoom call, a leader of a U.S.-based abortion rights group pledged \$4,000, adding that she hoped to make the same payment quarterly.

Cruz Sánchez declined to disclose her group's donors and said she has not been keeping detailed records of the money she has received from donors in the United States. Between 2009 and 2018, Las Libres received at least \$193,000 in public grants from the Mexican government, according to government records.

On its search for cheap pills, Las Libres determined that Mexico-based suppliers were too expensive. One set of mifepristone and misoprostol costs about 26 U.S. dollars in Mexico, Cruz Sánchez said. But in South Asia, pills are a fraction of that price, according to Chris Purdy, chairman of the board of DKT International, one of the largest organizations that registers, imports and distributes abortion pills around the world. In India, where many of the largest abortion-pill manufacturers are based, combo-packs of mifepristone and misoprostol are widely available at pharmacies for as little as \$1.50, Purdy said.

In mid-September, Cruz Sánchez boarded an overseas flight from Guanajuato, returning four days later with thousands of abortion pills. From there, Cruz Sánchez began sending the pills to towns along the U.S.-Mexico border, where volunteers were waiting to carry them into the United States.

When selling directly to patients, suppliers typically offer pills at a significant markup. Europe-based Aid Access prescribes and sells pills for just over \$100 per dose, sometimes offering discounts or free pills for low-income customers. Other online pharmacies charge hundreds of dollars. A medication abortion at a licensed U.S. clinic typically costs between \$500 and \$600, on top of the price of transportation and accommodations for those who have to travel out of state.

Cruz Sánchez says she will never charge patients for abortion pills, which she believes should be widely accessible to all. She is critical of organizations that sell pills to patients for more than they bought them for, accusing these groups of engaging in the "corporatization" of illegal abortions.

The Aid Access website invites people who can't afford to pay for the pills to "tell us," so the organization can help.

"Aid Access believes that a just and equal system means that women with the financial means can pay this way and also support the service for women who cannot afford to pay," Gomperts said.

While Gomperts and other Aid Access-affiliated physicians write prescriptions for abortion pills — and provide medical consultations to anyone who asks for assistance up to 12 weeks of pregnancy — Cruz Sánchez and her network of volunteers offer their own, more informal support services to women who need guidance while taking the pills. Cruz Sánchez has been expanding these connections, connecting with U.S.-based hotline services and medical professionals.

As far as she knows, Cruz Sánchez said, no one in the U.S. has had severe medical complications after receiving pills from Las Libres.

For most Americans working with Las Libres, Cruz Sánchez said, the more pressing concern is a legal one. Many of her U.S.-based volunteers are terrified of the prison sentence they could face if they get caught, adopting aliases and avoiding police.

Cruz Sánchez tells them not to worry.

"What's the government going to do? Open every package in the mail? Conduct an inspection inside every woman's home?"

"They don't have a way to do it," she'll say with a smile. "There's no way."

A lawyer defines the 'legal lines'

One thousand miles north, in Dallas, Tex., nearly 100 abortion rights advocates squeezed into a hotel conference room in late August to learn about the illegal abortion movement — and the risks of signing up.

The lawyer at the front of the room did not explicitly mention the abortion pills flowing into the U.S. from Mexico. But she singled out a group she calls "the helpers": people who are helping American women secure pills in antiabortion states.

This group was particularly vulnerable to legal risk, she said.

At a conference led by SisterSong, a national reproductive justice group, attendees flocked to this particular session, "Self-Managed Abortion in the US After Roe." Many in the room worked for abortion funds and other abortion rights groups, eager to bring what they learned back to their communities.

"Let's say this one together," the lawyer told the audience, gesturing to the all-caps message on the projector: "Don't talk to cops."

"One more time for the people outside."

The room reverberated with dozens of voices: "DON'T TALK TO COPS."

The lawyer leading the chants that day was Jill Adams, the executive director of If/When/How, an abortion rights group that in 2015 started supporting people prosecuted for ending their own pregnancies, or assisting in that process.

Staffed by over two dozen lawyers and bolstered by a network of law students, the organization runs a legal help line for those charged — and those who fear they might be charged. The hotline now receives 14 times more calls than it did before the Supreme Court decision, Adams said.

To get a sense of what their clients are facing, the group has been tracking pregnancy-related prosecutions over time. Between 2000 and 2020, 61 people were criminally investigated or arrested for either ending their own pregnancy or helping someone else end theirs, [according to a preliminary report](#) the organization published in August.

That number is likely a significant undercount, Adams said — and almost certain to climb now that the Supreme Court has overturned *Roe*.

Adams and her team don't know of anyone who has gone to jail for shepherding abortion pills since the June ruling, she said. But she warned that could start happening soon. While the new wave of abortion bans explicitly prohibit prosecutors from going after the people seeking abortions, volunteers caught securing or distributing abortion pills could be charged as abortion providers, Adams said — subject to the same punishment as a doctor who performed a surgical abortion at a shuttered clinic. Across much of the South and Midwest, that means at least several years in prison.

Adams, in an interview after the conference, said that If/When/How doesn't promote breaking the law.

"We don't encourage them," she said of her clients. "We just provide the information so they can conduct their own risk analysis. Our job is to make sure that everybody understands where the legal lines are drawn."

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The abortion pill pipeline creates a challenge for conservative state lawmakers, who had hoped the Supreme Court's ruling would be a major step toward eliminating abortion. With the push for self-managed abortions and increased funding available for out-of-state travel, Missouri state Rep. Mary Elizabeth Coleman (R) said in an interview that she expects the number of abortions to increase in the wake of *Roe*'s reversal.

"People don't know that it's happening," said Coleman, who has championed aggressive antiabortion legislation.

Now that strict new bans have taken effect across much of the country, some lawmakers have turned their attention to local prosecutors, eager to make sure their laws are enforced.

Once prosecutors realize the extent of the illegal activity, Coleman said, "they are going to be interested in making sure that the law is followed."

A distributor hosts a 'packing party'

By the time *Roe* was overturned, some abortion rights activists had been mailing pills illegally, without prescriptions, for years.

In one Republican-led state in the south, a leader of a high-profile abortion rights group launched her organization's "shadow side" in 2019, sending medication to women who couldn't make it to a clinic: Minors with antiabortion parents. Domestic violence victims trapped with abusive partners. Anyone who couldn't afford the high cost of clinic care.

When she first started out, the distributor mailed a few sets of pills a year.

Now, she mails 12 a day — more than the number of abortions performed at many clinics.

The distributor, in her sixties, messages Cruz Sánchez of Las Libres every few weeks to ask for more inventory. Once the pills arrive, she convenes what she calls "packing parties" at her suburban home, where she and her colleagues mete out the medication, dose by dose.

"It would be nice to be able to send them something more professional," the distributor said as she readied a new batch in early September, pouring 150 misoprostol pills out of a calcium bottle.

The pills she poured into a bowl were slightly different shapes and sizes. Some scored, others smooth. The distributor plucked out a few that had broken in half.

When she used to buy pills from various online pharmacies, the distributor said, they would arrive in individual blister packs, with an expiration date. But those were \$200 a set — and Cruz Sánchez sent hers for free.

"I want women to feel like it's legitimate," said another participant at the packing party, a younger activist. "Like they haven't just gotten drugs in a nightclub, you know?"

"Like we're not a back-street type of organization," said a third helper, an 80-year-old who had smuggled the pills from Mexico.

They did what they could to create a dignified operation in the distributor's living room. While the pills were out on the coffee table, the women would not eat. They would not drink wine. They would wear blue latex gloves.

"If I were taking pills that someone sent me, I'd hate to think that they'd been rumbling around in hands that might have just pet a dog," said the distributor, her fingers swirling around in the misoprostol.

The 80-year-old raised her eyebrows.

"I did?" said the distributor.

"Well, you know what?" said the younger activist, throwing up her hands. "We're not f---ing doctors, we're not health-care workers. Everyone is taking some risk in this somewhere along the line, and what can you do when it's illegal?"

Since *Roe* fell, the distributor has become a teacher of sorts for newcomers joining her in the abortion pill movement. Among her students was the clinic nurse who had recently begun distributing Las Libres pills after reconnecting with a patient at a grocery store. By the end of the summer, the nurse was receiving bulk shipments of 150 abortion pills and consulting with women across eight states.

On a call in late August, the distributor offered the nurse a long list of tips: Look up houses for sale to use as return addresses. Set your messages with Las Libres to delete after 24 hours. Absolutely never meet a patient in person. If you have legal questions, reach out to If/When/How.

"It's legally risky to do this," the distributor told the nurse. "You need to take every precaution possible."

As these networks expand, the distributor said, there will be even more to worry about. She said she recently saw a public service announcement issued by Ipas Partners for Reproductive Justice, the abortion rights nonprofit, warning about online abortion pill scammers — a message that echoed concerns frequently voiced by antiabortion advocates.

"We don't know what's coming in the mail," said Ingrid Skop, an OB/GYN and a senior fellow at the Charlotte Lozier Institute, an antiabortion organization. "We're inclined to think they're getting misoprostol and mifepristone — but are there contaminants in the drugs? Does it contain the quantities that is advertised?"

Asked if she worries about the authenticity of her pills, the distributor is quick to shake her head.

"I get them from a verified source," she says, her tone reverent: "Verónica," the founder of Las Libres.

With Cruz Sánchez's blessing, the distributor says, she has helped send pills to women as far as 15 weeks along in their pregnancies. Many in the medical community, including Brandi, the spokesperson for the American College of Obstetricians and Gynecologists, say it's safe to take abortion pills beyond the 10-week limit imposed by the FDA.

The distributor refers the later-term cases to an abortion doula she's known for years, who counsels them over text about exactly what they will see when they pass the pregnancy. A 12-week fetus is roughly the size of a plum; a 15-week fetus, the size of an apple.

These cases, in particular, present significant legal risk to the patient, who has to figure out how to surreptitiously dispose of the remains. The abortion doula said she often sends a small amount of acid so the client can dissolve some of the fetus, and bury whatever is left.

"I try to emotionally prepare them and say, 'It's going to look like a baby,'" the doula said.

The distributor has seen enough of these complex cases to know how to respond, she said. She worries about the new volunteers joining the movement: eager to help, but green.

"Someone is going to end up getting less than ideal treatment, and someone is probably going to get arrested," the distributor said. "There are just so many things that could go wrong."

Sitting in her living room, the distributor shook her head and sighed: Time to focus on the things she could control. She powered up her burner phone and logged into her Proton Mail account, an encrypted email service she uses to correspond with patients who need pills.

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Some of the women get her contact information from Cruz Sánchez. A few hear through a friend, or a friend of a friend. One of the biggest spikes in demand came after the distributor met several volunteers who offer advice in a Reddit forum frequented by anonymous women searching for abortion care.

“I can handle more traffic,” the distributor had told the volunteers.

She immediately started mailing packages to Reddit users — answering their frantic calls for help.

A woman takes the pills

Monica’s cramps didn’t start until she took the second set of pills on a Sunday morning. She said she lay down in bed as soon as she felt the first one coming on, wearing her favorite oversized T-shirt and a diaper pad.

This was her first pregnancy, but Monica imagined this was what contractions might feel like: intense pain, a few minutes of relief, then more pain — each wave of cramping a little worse than the one before. Balled up in the fetal position, she said she called a friend who’d had a medication abortion a few years before at Planned Parenthood, with a doctor beside her.

“Dude, I don’t know if this is normal,” her friend said when Monica described the pain. “Maybe you should go to the hospital.”

But Monica couldn’t go to the hospital — surely, she thought, the doctors would know what she’d done and report her. Her boyfriend threw some clothes in a bag anyway.

“Turn on the bath,” Monica said she yelled out to him. “I need to get in there.”

She felt a flood of liquid in her underwear and stepped into the bath with her clothes still on. Lying back in the tub, she said, she felt some pressure release. Then she screamed.

The fetus was floating in the water. Slightly smaller than her palm, the fetus had a head, hands, and legs, she said. Defined fingers and toes.

She leapt from the bath and collapsed in her boyfriend’s arms. Desperate for some guidance, soaking wet and crying, she took out her phone.

“I just passed the fetus,” Monica wrote to whomever had sent her the pills. She learned later that her fetus matched descriptions of those roughly 13 weeks along, well beyond the 10-week cap set by the FDA for taking abortion pills.

“I’m just feeling a little scared,” she added.

The anonymous user, whose identity is not known by The Post, immediately started typing. Everything would be okay, they assured Monica: The worst was over. Whatever she was feeling — sadness, relief, grief, anger — it was all normal.

“Going through an abortion can bring up a lot of emotions,” they wrote. “Just take some time for yourself.”

Three hours later, Monica said, she and her boyfriend selected a tree in a quiet corner of their favorite park — far enough back in the forest, they hoped, that a dog wouldn’t catch the scent. While most people flushed the fetus down the toilet, the Reddit user had told her, others preferred to do some kind of ritual.

Monica knew she wanted to say goodbye.

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When she was ready, she gathered a handful of wildflowers. Her boyfriend dug a small hole. As Monica lowered the cardboard box into the ground, she said, she knew she'd made the right choice. She couldn't give that fetus a good life yet, she thought to herself. She wasn't ready to be a mom.

"I hope in the future, when I am ready, your soul will find me again," Monica remembers saying as she knelt in the dirt.

"It just wasn't our time."

Story editing by Peter Wallsten. Photo editing by Natalia Jiménez-Stuard. Copy editing by Sam-Omar Hall. Design by Madison Walls. Alice Crites, Mary Beth Sheridan, Nora D. Palma, Alejandra Ibarra Chaoul, Danielle Villasana, Antonio Campos Ayala and Gabriela Montejano Navarro contributed to this report.

EXHIBIT 15

FDA 2002 Citizen Petition of AAPLOG

**BEFORE THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

536 02 AUG 20 P1 55

5 **Citizen Petition re: Request for**)
Stay and Repeal of the Approval of)
Mifeprex (mifepristone) for the Medical)
Termination of Intrauterine Pregnancy)
10 **through 49 Days' Gestation**)

CITIZEN PETITION AND REQUEST FOR ADMINISTRATIVE STAY

The American Association of Pro Life Obstetricians and Gynecologists ("AAPLOG"),
15 the Christian Medical Association ("CMA"), and Concerned Women for America ("CWA")
(collectively, "the Petitioners") submit this Petition pursuant to 21 C.F.R. §§ 10.30 and 10.35;
21 C.F.R. Part 314, Subpart H (§§ 314.500-314.560); and Section 505 of the Federal Food, Drug
and Cosmetic Act (21 U.S.C. § 355).¹ The Petitioners urge the Commissioner of Food and Drugs
to impose an immediate stay of the approval by the Food and Drug Administration ("FDA" or
20 "agency") of MifeprexTM (mifepristone; also, "RU-486"),² thereby halting all distribution and
marketing of the drug, pending final action on this Petition. In addition the Petitioners urge the
Commissioner to revoke FDA's approval of Mifeprex and request a full FDA audit of the
Mifeprex clinical studies.³

¹ Federal Food, Drug, & Cosmetic Act of 1938 ("FD&C Act"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

² The New Drug Application for Mifeprex, which was filed by the Population Council, was approved on September 28, 2000. Mifeprex is distributed by Danco Laboratories, a licensee of the Population Council.

³ The Petitioners will, at times, cite to documents contained in FDA's January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act request ("FDA FOIA Release") filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <<http://www.fda.gov/cder/archives/mifepristone/default.htm>>. Since the initial release FDA has edited some of the 94 files. However, the stamped page numbers have not changed. Additionally, many footnotes refer to Appendix A to this Petition, which contains a selected bibliography.

02P-0377

App. 000311 CP 1

I. ACTION REQUESTED

The Petitioners respectfully request that the Commissioner immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on this Petition. They urge the Commissioner to revoke market approval for Mifeprex in light of the legal violations and important safety concerns explained below. In addition, they request a full FDA audit of all records from the French and American clinical trials offered in support of the Mifeprex NDA.

II. INTEREST OF THE PETITIONERS

While it is true that the Petitioners have consistently opposed abortion and continue to do so, a careful examination of the claims made in this petition should alert people of conscience on either side of this issue that women are being harmed. Regardless of one's position on abortion, FDA's violations of its standards and rules have put women's health and lives at risk. The Petitioners are non-profit organizations that share a great concern about women's health issues. The American Association of Pro-Life Obstetricians and Gynecologists ("AAPLOG") is a recognized interest group of the American College of Obstetricians and Gynecologists ("ACOG"), currently representing over 2,000 obstetricians and gynecologists throughout the United States of America. The Christian Medical Association, founded in 1931, is a professional organization with thousands of physician members representing every medical specialty. Concerned Women for America ("CWA"), founded in 1979, is the largest public policy women's organization in the United States with members in every State and a total membership exceeding 500,000.

III. STATEMENT OF GROUNDS

A. SUMMARY OF THE PETITIONERS' ARGUMENTS

5 Good cause exists to grant an immediate stay of the agency's September 28, 2000
Mifeprex approval.⁴ Good cause also exists for the subsequent revocation of that approval.⁵ As
established herein, (1) the approval of Mifeprex violated the Administrative Procedure Act's
prohibition on agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not
in accordance with law;⁶ (2) FDA's approval of Mifeprex violated 21 U.S.C. § 355 because the
10 drug does not satisfy the safety and labeling requirements of that section; and (3) the agency
approved Mifeprex despite the presence of substantial risks to women's health.

This Petition represents the latest attempt by members of the medical community and
other concerned observers to warn FDA of the dangers posed by Mifeprex abortions to the health
of women.⁷ Women undergoing Mifeprex abortions risk, among other problems, uncontrolled
15 fatal hemorrhage and serious bacterial infections. Mifeprex abortions particularly endanger
women with ectopic pregnancies and those whose pregnancies have progressed beyond 49 days.⁸

⁴ When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Petition, "Mifeprex Regimen" will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

⁵ See 21 C.F.R. § 314.530 ("Withdrawal Procedures").

⁶ 5 U.S.C. § 706(2)(A).

⁷ On February 28, 1995, Americans United for Life and other groups and individuals filed a Citizen Petition with FDA requesting it to "refuse to approve any NDA for RU 486 for use as a pharmaceutical abortifacient that does not contain adequate evidence that the drug has undergone nonclinical and clinical safety and effectiveness trials." The petitioners also set forth a number of factors for the agency to consider. Americans United for Life *et al.*, Citizen Petition (Feb. 28 1995)[FDA FOIA Release: MIF 006144-6248]; *see also*, Letter, Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Gary L. Yingling, McKenna & Cuneo (March 20, 1995) (one-page letter suggesting that the petition was prematurely filed and claiming to be a "full response") [FDA FOIA Release: MIF 006250].

⁸ The gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy. On Day 49, a woman is deemed to be seven weeks pregnant, which means she has experienced 49 days of amenorrhea (time elapsed since the beginning of her last menstrual period).

Warnings about these dangers, together with FDA's own concerns about the safety of the abortion regimen, went unheeded. On September 28, 2000, FDA approved the new drug application ("NDA") for Mifeprex.⁹ The initial reports of life-threatening and fatal adverse events appear to bear out the safety concerns underlying the pre-approval warnings. The Petition

5 highlights a number of agency actions that were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. These serious departures from standard agency practice allowed the NDA for Mifeprex, a drug that is not safe for its intended use, to be approved by FDA.¹⁰

First, the approval of Mifeprex violated the legal requirements of FDA's Accelerated

10 Approval Regulations found in Subpart H.¹¹ Mifeprex is not a drug for the treatment of a serious or life-threatening illness. It does not demonstrate the potential to address an unmet medical need because a less dangerous and more effective alternative for performing abortions already exists. It appears that FDA's decision to use Subpart H was motivated by its concern that, without restrictions, the drug could not be used safely. Rather than attempting to compensate for

Ovulation for the small percentage of woman with a perfect 28 day cycle typically takes place between Days 12 and 14 and fertilization typically takes place 24 to 48 hours later.

⁹ See U.S. Department of Health and Human Services, *HHS News*, Press Release P00-19, "FDA Approves Mifepristone for the Termination of Early Pregnancy," September 28, 2000. A selection of FDA documents relevant to its approval of Mifeprex may found at: <<http://www.fda.gov/cder/drug/infopage/mifepristone>>; and on a second page: <http://www.fda.gov/cder/foi/nda/2000/20687_mifepristone.htm>.

¹⁰ FDA's unlawful approval of Mifeprex may not be unprecedented. The medical-scientific community and the mainstream press have called attention to a number of other instances in which one could question whether drugs and medical devices have been improperly approved. See, e.g., Richard Horton, "Lotronex and the FDA: A Fatal Erosion of Integrity," *Lancet* 357 (May 19, 2001): 1544-1545; David Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times* (Dec. 20, 2000): at A1; Kit R. Roane, "Replacement Parts: How the FDA Allows Faulty, and Sometimes Dangerous, Medical Devices onto the Market," *U.S. News & World Report* (July 29, 2002): 54-59 (discussing FDA's recent approval policies regarding medical devices).

¹¹ 21 C.F.R. §§ 314.500-314.560. FDA's Accelerated Approval Regulations are set forth at 21 C.F.R. Part 314, Subpart H ("Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses") ("Accelerated Approval Regulations" or "Subpart H"). The Accelerated Approval Regulations were promulgated by FDA after notice and comment: New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234 (April 15, 1992) ("Subpart H Proposed Rule") and New Drug, Antibiotic, and Biological

the inherent dangerousness of Mifeprex by inappropriately resorting to the Subpart H approval mechanism, FDA should simply have refused to approve Mifeprex. (*See* Section III.D., *infra.*)

Second, Mifeprex was not proven to be “safe and effective” as required by law.¹² The scientific quality of the trials used to support the NDA was undeniably deficient according to Congress’s statutory requirements and FDA’s well-established standards.¹³ The trials were not blinded, randomized, or concurrently controlled. FDA failed to explicitly waive its rules or offer a reasoned explanation for defying its own standards. (*See* Section III.E., *infra.*)

Third, the Mifeprex Regimen requires that Mifeprex be used in conjunction with another drug, misoprostol. FDA, however, has never approved misoprostol as an abortifacient.

Although FDA normally opposes the promotion of off-label uses, in connection with the Mifeprex NDA, the agency sanctioned and itself participated in the promotion of the off-label use of misoprostol. Mifeprex, the label of which creates the false impression that misoprostol is approved for use as an abortifacient, is misbranded. (*See* Section III.F., *infra.*)

Fourth, and most critically, the Mifeprex Regimen is dangerous. FDA sought, without success, to convince the drug sponsor to place safety restrictions on Mifeprex. When that failed, on June 1, 2000, FDA itself proposed restrictions intended to reduce the unacceptable health risks associated with mifepristone abortions. Nevertheless, the agency, under concerted pressure from abortion advocates and politicians, ultimately approved mifepristone for use in a deregulated regimen that lacks key safeguards. For example, the regimen does not include a requirement that transvaginal ultrasound be used to date pregnancies and rule out ectopic

Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942 (Dec. 11, 1992) (“*Subpart H Final Rule*”) (available at: <<http://www.fda.gov/cder/fedreg/fr19921211.txt>>).

¹² *See* 21 U.S.C. § 355.

¹³ *See* 21 C.F.R. § 314.126.

pregnancies, which cannot be treated with the Mifeprex Regimen. In addition, FDA failed to restrict access to mifepristone to physicians trained in the provision of Mifeprex and surgical abortions and capable of treating complications arising from abortions. Concerns about the dangers of Mifeprex were confirmed when Danco and FDA announced publicly on April 17, 2002, a number of serious adverse events, including two deaths. (*See* Section III.G., *infra*.)

Fifth, the drug's sponsor has neglected to require Mifeprex providers to adhere to the limited restrictions contained in the approved regimen. The sponsor's inaction is surprising in light of the fact that these restrictions are being flouted openly. Section 314.530 authorizes FDA to withdraw the approval of a Subpart H drug if a drug's sponsor does not fulfill its responsibility of ensuring compliance with the restrictions on the use of the drug. (*See* Section III.H., *infra*.)

Sixth, the safeguards employed in the U.S. Clinical Trial are not mirrored in the regimen that FDA approved. Transvaginal ultrasounds, for example, although employed in the U.S. Clinical Trial, are not required under FDA's approved regimen. Nor are the trial requirements governing emergency care reproduced in the approved regimen. (*See* Section III.I., *infra*.)

Seventh, FDA's waiver of its rule, 21 C.F.R. § 314.55, requiring the testing of all new drugs for their potential effects on children, has jeopardized the health and safety of American teenage girls who may have abortions. FDA expressly contemplated the pediatric use of Mifeprex, but waived, without an adequately reasoned justification, the requirement that the drug undergo pediatric testing. (*See* Section III.J., *infra*.)

Eighth, FDA did not require the sponsor of Mifeprex to honor its commitments for Phase IV studies, which provide the opportunity to study in-depth the drug's safety and effectiveness after approval. When FDA approved Mifeprex, the agency permitted the Population Council to replace the six Phase IV study commitments it had made in 1996 with two much narrower

commitments. The modified studies will not adequately address outstanding questions, such as the effects of mifepristone abortions on women outside the tested age range of 18 to 35 years.

(See Section III.K., *infra*.)

In sum, FDA, in approving Mifeprex, acted in a manner inconsistent with its statutory authorization, regulations, and well-established policies. FDA did not provide a contemporaneous explanation of its numerous departures from past practice.¹⁴ Its aberrant actions coupled with the absence of explanations violated a fundamental principle of administrative law; an agency must either adhere to prior policies or fully explain why it is not doing so.¹⁵ The approval of Mifeprex was, therefore, arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. It must be reversed.

B. FDA APPROVAL OF THE MIFEPREX REGIMEN

1. The Introduction of Mifepristone into the United States

Roussel Uclaf, a French pharmaceutical firm, first developed and tested mifepristone (“RU-486”) as an abortifacient. By April 1990 the drug had become permanently available in

¹⁴ An agency must explain its reasons for acting in a particular manner. See, e.g., *Securities & Exchange Commission v. Chenery Corp.*, 332 U.S. 194, 196-97 (1947) (noting that a court should not “be compelled to guess at the theory underlying the agency’s action,” but rather “[i]f the administrative action is to be tested by the basis upon which it purports to rest, that basis must be set forth with such clarity as to be understandable.”). *Post hoc* rationalizations cannot salvage the agency’s action with respect to Mifeprex. See, e.g., *Martin v. Occupational Safety and Health Review Commission*, 499 U.S. 144, 156-57 (1991) (*post hoc* rationalizations of counsel “do not constitute an exercise of the agency’s delegated lawmaking powers”); *Investment Company Institute v. Camp*, 401 U.S. 617, 628 (1971) (“Congress has delegated to the administrative official and not to appellate counsel the responsibility for elaborating and enforcing statutory commands.”).

¹⁵ See, e.g., *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970) (“[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute.”) (footnote omitted) (citing approvingly *Motor Vehicle Manufacturers Ass’n v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 57 (1983)); *JSG Trading Corp. v. USDA*, 176 F.3d 535, 544 and 545 (D.C. Cir. 1999) (remanding agency action where “the agency manifestly failed to explain its abrupt departure from prior precedent” and noting that the agency “was obligated to articulate a principled rationale for departing from [its prior] test”) (citations omitted); *Gilbert v. National Labor Relations Board*, 56 F.3d 1438, 1445 (D.C. Cir. 1995) (“It is, of course, elementary that an agency must conform to its prior decisions or explain the reason for its departure from such precedent.”).

France. According to Dr. André Ulmann, the Roussel project manager for the development of RU-486, Roussel prohibited the commencement of any new studies in the United States and took the position that “under no circumstance[s]” would it permit a new drug application to be filed with FDA.¹⁶ In fact, “the chairman of Hoechst [the parent company to Roussel] had officially
 5 declared that mifepristone was not compatible with the ethics of the company.”¹⁷

Undeterred by Hoechst’s reluctance to bring the drug to the United States, on January 22, 1993, President Clinton directed Department of Health and Human Services (“HHS”) Secretary Donna Shalala to assess initiatives to promote the testing and licensing of mifepristone or other antiprogestins in the United States.¹⁸ Further signaling that approval of mifepristone by FDA
 10 was a top priority of his Administration, President Clinton reportedly “wrote to Hoechst asking the company to file a new drug application with the FDA (an unprecedented situation in the pharmaceutical industry!), which Hoechst intransigently refused to do.”¹⁹

In early 1993, Secretary Shalala and FDA Commissioner David Kessler “communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the
 15 American marketplace.”²⁰ On May 16, 1994, the Population Council reached an agreement with Roussel Uclaf, pursuant to which the European drug maker transferred “without remuneration,

¹⁶ See André Ulmann, M.D., “The Development of Mifepristone: A Pharmaceutical Drama in Three Acts,” *Journal of the American Medical Women’s Association* 55 (Supplement 2000): 117-20, at 119. In 1994 Roussel Uclaf joined with the German pharmaceutical firm, Hoechst AG, to form Hoechst Roussel Ltd. In 1995, this entity merged with a third firm, Marion Merrell Dow, to form Hoechst Marion Roussel. In December 1999 Hoechst and Rhône-Poulenc combined to form Aventis, S.A., headquartered in Strasbourg, France.

¹⁷ Ulmann, *infra* Appendix A, at 120.

¹⁸ See Memorandum for the Secretary of Health and Human Services, “Importation of RU-486,” *Public Papers of the Presidents: Administration of William J. Clinton*, 1993 (Jan. 22, 1993) at 11.

¹⁹ Ulmann, *infra* Appendix A, at 120 (emphasis in original).

²⁰ HHS Fact Sheet, “Mifepristone (RU-486): Brief Overview,” (rel. May 16, 1994). Available at: <<http://www.hhs.gov/news/press/pre1995pres/940516.txt>>.

its United States patent rights for mifepristone (RU-486) to the Population Council”²¹

Secretary Shalala was instrumental in bringing about the transfer of the patent rights to the Population Council²² and even set a deadline – May 15, 1994 – for the transfer.²³

After obtaining the American patent rights to mifepristone, the Population Council
 5 conducted clinical trials in the United States and filed a new drug application in 1996. The
 Population Council established a non-profit corporation, American Health Technologies
 (“AHT”), to assist in the effort to bring the drug to the market.²⁴ The Population Council
 ultimately granted Danco Laboratories, LLC (“Danco”), which was incorporated in the Cayman
 Islands in 1995, “an exclusive license to manufacture, market, and distribute Mifeprex in the
 10 United States.”²⁵ Danco, after a difficult search,²⁶ selected the Chinese drug manufacturer,

²¹ HHS Press Release, “Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council,” (rel. May 16, 1994). Available at: <<http://www.hhs.gov/news/press/pre1995pres/940516.txt>>.

²² *Id.* (“Shalala commended Roussel Uclaf and the Population Council for coming to closure after months of complex negotiations amid repeated urging from the Clinton administration.”)

²³ See William J. Eaton, “Path Cleared for Abortion Pill Use Medicine: French Maker of RU-486 Gives Patent Rights to a Nonprofit Group,” *Los Angeles Times*, May 17, 1994, at A1 (“Negotiations between the French manufacturer and the Population Council dragged on for more than a year until Shalala set a May 15 deadline, producing the agreement . . .”).

²⁴ Dr. Susan Allen, who once served as president and CEO of American Health Technologies, joined the staff of the Reproductive and Urologic Drug Products Division in FDA’s Center for Drug Evaluation and Research in 1998 as a medical officer and was promoted to team leader for reproductive drugs in January 1999. See “RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director,” *The Pink Sheet* 62 (June 12, 2000): at 14. Dr. Allen became acting director of the Division in January 2000 and permanent director on June 18, 2000. See *id.* *The Pink Sheet* also commented, “Allen is presumably recused from the mifepristone review as a result of her prior experience with the product.” *Id.*

²⁵ Danco, “The History of Mifeprex,” available at <<http://www.earlyoptionpill.com/history.php3>>. (Danco has dubbed mifepristone “the Early Option Pill” for marketing purposes.) Little information about Danco is available. See Robert O’Harrow, “RU-486 Marketer Remains Elusive,” *Washington Post* (Oct. 12, 2000): at A18 (“Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry.”). Danco is apparently a successor entity to Advanced Health Technology. See “RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director,” *The Pink Sheet* 62 (June 12, 2000): at 14 (reporting that Advanced Health Technologies had become Neogen, which, in turn, had become Danco, according to the Population Council and Danco, “with some management and investor changes”).

²⁶ In 1995 Danco contracted with a Hungarian pharmaceutical firm, Gideon Richter, to manufacture mifepristone for American distribution. After Gideon Richter reneged on the contract in February 1997, Danco sued Gideon Richter for breach of contract and began searching for a new producer. See “Ru-486: U.S. Partners Sue European Manufacturer,” *Kaiser Daily Reproductive Health Report* (June 12, 1997) (available at: <<http://www.kaisernetwork.org/reports/1997/06/a970612.1.html>>). This was one of a number of lawsuits stemming

Shanghai Hua Lin Pharmaceutical Company, to manufacture the drug.²⁷ Abortion advocates eagerly awaited the approval of mifepristone in the United States because, among other reasons, they anticipated that it would enhance women's access to abortion.²⁸

5

2. FDA Approval of Mifepristone

The Population Council filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.²⁹ FDA initially accorded the drug standard review, but in a letter dated May 7, 1996, FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.³⁰ On September 18, 1996, FDA issued a letter

from attempts to bring mifepristone to the United States. See "Ru-486: Litigation Could Cause Delay For U.S. Introduction," *Kaiser Daily Reproductive Health Report* (Dec. 17, 1996) (available at: <<http://www.kaisernetwork.org/reports/1996/12/a961217.9.html>>) (describing some of the legal problems encountered by the Population Council in bringing the drug to market).

²⁷ Pamela Wiley, "Chinese Plant to Make RU-486 for U.S.," (Oct. 15, 2000) (available at: <<http://www.nurseweek.com/news/00-10/1015-486.asp>>).

²⁸ See Margaret Talbot, "The Little White Bombshell," *New York Times Magazine* (July 11, 1999): at 39-43 ("One of my real, and I think realistic, hopes for this method," says Carolyn Westhoff, an OB-GYN at Columbia University medical school who offers medical abortion as part of a clinical trial, 'is that it will help get abortion back into the medical mainstream and out of this ghettoized place it's been in.' And if that is indeed the scenario we're looking at – a scenario in which abortion is folded far more seamlessly into regular medical practice – then it has implications not only for women's experience of abortion but for the politics of abortion as well."); *id.* ("Not only are mifepristone abortions, by nature, more discreet than their surgical equivalents (like vacuum aspiration), but the practitioners who prescribe them will almost certainly constitute a larger and a more varied group than the dwindling corps of OB-GYNs willing to do surgical abortions.") In fact, access to medical abortion, will continue to depend on the availability of surgical abortion, which serves as a back-up in FDA's approved Mifeprex regimen. Thus, it is spurious to suggest that Mifprex abortions can safely be made available in places in which surgical abortion is not offered.

²⁹ The application was dated March 14, 1996 and received by FDA on March 18, 1996. See Letter, FDA/CDER to Ann Robbins, Population Council (Sept. 18, 1996): at 1 ("1996 Mifepristone Approvable Letter").

³⁰ See Letter, FDA/CDER to Ann Robins, Population Council (May 7, 1996)[FDA FOIA Release: MIF 006431]. The Population Council filed its complete response on March 30, 2000, which gave FDA until September 30, 2000 to act on the application. In fiscal year 2000 a "standard" designation would have given FDA at least ten months to consider the application. FDA accorded mifepristone "priority review," which typically required FDA to act within six months. See FDA/CDER, "PDUFA Reauthorization Performance Goals and Procedures" (Nov. 16, 1997) (available at: <<http://www.fda.gov/cder/news/pdufagoals.htm>>) ("Fiscal Year 2000"). Of 98 approvals in 2000, only 20 were Priority Review drugs. See FDA/CDER, *Report to the Nation* (2000): at 6. FDA's use of priority review appears inappropriate when considered in light of the agency's current guidance on the issue, which states that priority review is appropriate when "[t]he drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease." See FDA/CDER, "Review Management: Priority Review Policy," Manual of Policies and Procedures (MAPP) 6020.3, at 1 (Apr. 22, 1996) (text bracketed as in original).

stating that the application was approvable and requested more information from the sponsor.³¹

FDA issued a second approvable letter for mifepristone, dated February 18, 2000, setting forth the remaining prerequisites for approval.³² The 2000 Mifepristone Approvable Letter announced that FDA had “considered this application under the restricted distribution regulations contained
5 in 21 CFR 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product.”³³

On September 28, 2000, FDA approved mifepristone (“MifeprexTM”) “for the medical termination of intrauterine pregnancies through 49 days’ pregnancy.”³⁴ Mifeprex was approved under Subpart H, which, FDA explained, “applies when FDA concludes that a drug product
10 shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with certain skills or experience.”³⁵ The approved regimen requires at least three office visits.³⁶ FDA required the Population Council to include, on the Mifeprex Label, a “black box warning for special problems, particularly those that may lead to death or serious injury.”³⁷

³¹ 1996 Mifepristone Approvable Letter at 1.

³² 2000 Mifepristone Approvable Letter at 1.

³³ 2000 Mifepristone Approvable Letter at 5.

³⁴ Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 1 (“Mifeprex Approval Letter”). In conjunction with the Mifeprex Approval Letter, FDA issued a memorandum that expanded upon the basis for and the restrictions on the approval of Mifeprex. *See* Memorandum, FDA/CDER to “NDA 20-687 MIFEPREX (mifepristone) Population Council” (Sept. 28, 2000): at 6 (“Mifeprex Approval Memo”).

³⁵ Mifeprex Approval Memo at 6.

³⁶ Pursuant to the approved regimen, on “Day One: Mifeprex Administration” the patient reads the Medication Guide, signs the Patient Agreement, and ingests 600 mg of Mifeprex; on “Day Three: Misoprostol Administration” the patient ingests 400 micrograms of misoprostol orally (unless abortion has occurred and been confirmed by clinical examination or ultrasonographic scan); and, on or about “Day 14: Post-Treatment Examination” the patient returns to the practitioner for verification through a clinical examination or ultrasound that the pregnancy has been successfully terminated. *See* Mifeprex Label (“Dosage and Administration”)(available at: <<http://www.fda.gov/cder/foi/label/2000/20687lbl.pdf>>).

³⁷ Mifeprex Approval Memo at 2 (citing 21 CFR 201.57(e), which authorizes FDA to require such a warning). The terms “label,” “labeling,” and “package insert” are often used interchangeably in food and drug law literature. In this Petition, “Label” describes the fine-print “package insert” that accompanies a drug when it is purchased. However, the FD&C Act defines “label” as “a display of written, printed, or graphic matter upon the immediate container of any article . . .” 21 U.S.C. § 321(k). The term “labeling,” which will also appear in this Petition,

FDA also outlined the Population Council's post-approval, Phase IV study commitments³⁸ and waived, without explanation, FDA's regulations providing that all new drugs must be tested for safety and effectiveness in children.³⁹

5 C. BACKGROUND ON FDA'S DRUG APPROVAL PROCESS

1. FDA's Default Rules for Establishing Drug Safety and Effectiveness

FDA's regulations state that "[t]he purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."⁴⁰ FDA's default criteria for establishing safety and effectiveness are commonly referred to as the agency's "gold standard."⁴¹ At the core of this default standard is FDA's recognition, reflecting the development of the scientific method and its application to pharmacology, that human bias and misperceptions are pervasive and that every precaution must be taken to avoid them. "The history of experimental medicine and research psychology," Michael Greenberg writes, "had demonstrated that uncontrolled, unblinded clinical trials were systematically vulnerable to experimenter bias, placebo effects, and the like."⁴² Consequently, rigorous policies have been set forth by FDA and,

encompasses "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). "Labeling" may even describe promotional materials used by the drug manufacturer including "[b]rochures, booklets, mailing pieces, . . . price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, . . . and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses . . ." 21 C.F.R. § 202.1(f)(2). FDA has provided more information on this terminology at: <<http://www.fda.gov/cder/handbook/adverdef.htm>>.

³⁸ See Mifeprex Approval Memo at 7.

³⁹ See FDA Mifeprex Approval Letter at 3.

⁴⁰ 21 C.F.R. § 314.126(a).

⁴¹ See Jennifer Kulynych, "Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 127-149, at 129. We will refer to these criteria as the "default standard."

⁴² Michael D. Greenberg, "AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process," *Legislation and Public Policy* 3 (2000): 295-350, at 308.

more recently, by the International Conference on Harmonisation (“ICH”) to eliminate bias from the evaluation of drug safety and effectiveness.⁴³

FDA has been criticized for its zealous implementation of this policy,⁴⁴ but there is widespread recognition of the value of the default standard. The 1962 statutory amendments to the FD&C Act “authorized the agency to review all NDAs, not only to assess drug safety, but also to determine whether a manufacturer has provided ‘substantial evidence’ from ‘adequate and well-controlled investigations’ that a drug is effective for its intended use.”⁴⁵ In implementing regulations, FDA “required that the evidence include at least one (and usually two) well-controlled (preferably ‘blind’) trials showing statistically significant results for treatment of humans with the new drug.”⁴⁶ “[B]arring unusual circumstances, the agency ordinarily requires two successful and well-controlled clinical trials for new drug approval.”⁴⁷ FDA’s mandate for clinical trials “has two very important elements:”

- (1) a “controlled” trial, in which an experimental drug is compared to a placebo, or a known effective treatment in order to establish the comparative efficacy of the drug, and
- (2) a “double-blind” trial, which involves random assignment of research subjects to the

⁴³ FDA, “International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials,” Notice, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The homepage, (www.ich.org), for the ICH describes the organization as follows: “The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.”

⁴⁴ See, e.g., Henry I. Miller, “Failed FDA Reform,” *Regulation* 21 (Summer 1998): 24-30.

⁴⁵ Kulynych, *infra* Appendix A, at 129 (citing 21 U.S.C. § 355(d)).

⁴⁶ Greenberg, *infra* Appendix A, at 307 (citing 21 C.F.R. § 314.126 (1999)). FDA comprehensively revised NDA evaluation rules in what is commonly referred to as the “NDA Rewrite.” See *Final Rule*, “New Drug and Antibiotic Regulations,” 50 Fed. Reg. 7452 (Feb. 22, 1985). Section 314.126 was promulgated in that final rule. *Id.* at 7506-7.

⁴⁷ Kulynych, *infra* Appendix A, at 130.

experimental and control groups, under conditions in which neither the doctors nor the research subjects know who is getting the experimental drug and who the control.⁴⁸

Each of the mandated features helps to eliminate bias in trial results. First, in “double-blinded” studies neither the patient nor the provider team (physician, nurse, etc.) knows the identity of the drug administered. If that is not possible, the person evaluating the trial results will not know which treatment has been administered to which subject. Second, a “randomized” study requires a random determination of which subject receives which treatment. This determination is often effected through computer-generated assignments done before clinical testing begins. Finally, comparison-control (also known as “comparator-control”) requires that the experimental drug be compared *concurrently* to the current best treatment, or, alternatively, to a placebo. A placebo is used when the drug being tested represents the first treatment of its kind for the particular indication and no established treatment exists.

2. FDA Initiatives to Expedite the Approval of Drugs for the Very Sick

Largely in response to FDA’s perceived slowness in approving drugs for human immunodeficiency virus (“HIV”) patients, the agency undertook several initiatives to either expedite the ability of seriously or terminally-ill patients to have access to experimental drugs or to provide processes “intended to move drugs to market more quickly by compressing clinical development and FDA review times.”⁴⁹ In 1988, FDA adopted an interim rule establishing Subpart E of 21 C.F.R. Part 312 (“Drugs Intended to Treat Life-Threatening and Severely-

⁴⁸ Greenberg, *infra* Appendix A, at 307-8 (footnotes omitted).

⁴⁹ Sheila R. Shulman and Jeffrey S. Brown, “The Food and Drug Administration’s Early Access and Fast-Track Approval Initiatives: How Have They Worked?” *Food and Drug Law Journal* 50 (1995): 503-531, at 503-4.

Debilitating Diseases”).⁵⁰ Subpart E embodied several of the new procedures that FDA had used to bring the HIV medication, AZT (zidovudine), to market quickly.⁵¹ Subpart E also created a “collaborative framework in which early and repeated consultation between the FDA and pharmaceutical manufacturers served to facilitate clinical trials, and to insure ex ante that prospective research designs would meet with subsequent regulatory approval.”⁵² “Taken together,” the innovations found in Subpart E, “served to radically alter the new drug approval process with regard to life-threatening illnesses, particularly for AIDS.”⁵³

On April 15, 1992, FDA took its procedural innovations further when it proposed an “Accelerated Approval” process (*i.e.*, Subpart H). Shulman and Brown believe that Subpart H “represent[ed] the most significant departure from the traditional FDA standards for drug approval.”⁵⁴ Subpart H’s “major point of departure” from previously existing approval regimes was its focus on granting drug approval “on the basis of the drug’s effect on a surrogate endpoint that is reasonably likely to predict clinical benefit over time.”⁵⁵ A “surrogate end point” or “surrogate marker” is “a laboratory parameter or physical sign that is used in a clinical trial as a substitute for a clinically meaningful end point, such as mortality.”⁵⁶ The value of surrogate

⁵⁰ See *Interim Rule*, “Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses,” 53 Fed. Reg. 41,516 (Oct. 21, 1988). The Subpart E rules may be found at 21 C.F.R. §§ 312.80-88.

⁵¹ See Greenberg, *infra* Appendix A, at 321.

⁵² Greenberg, *infra* Appendix A, at 321 (citation omitted).

⁵³ Greenberg, *infra* Appendix A, at 323.

⁵⁴ Shulman and Brown, *infra* Appendix A, at 514.

⁵⁵ Shulman and Brown, *infra* Appendix A, at 514. Likewise, Greenberg observed that the “essential element of the accelerated approval regulations [*i.e.*, Subpart H] was the provision that ‘surrogate endpoints’ could be employed as the empirical basis for FDA approval of a new drug.” Greenberg, *infra* Appendix A, at 323 (citation omitted).

⁵⁶ Dennis F. Thompson, “Surrogate End Points, Skepticism, and the CAST Study,” editorial, *Annals of Pharmacotherapy*, 36 (Jan. 2002): 170-71, at 170 (citations omitted).

endpoints lies in their ability to predict clinical outcomes.⁵⁷ As “examples of surrogate end points that have been proven to be excellent predictors of clinical outcomes and, hence, have saved both money and precious time expediting drugs to the patient care arena,” Dean Dennis Thompson cites “a diverse group of antihypertensive drugs approved on the basis of reduced blood pressure effects [that] has shown clear benefits in reducing cardiovascular events and mortality.”⁵⁸ With the passage of the Food and Drug Administration Modernization Act of 1997 (“FDAMA”), Congress effectively codified Section 314.510, the surrogate endpoint provision of Subpart H.⁵⁹

Neither Shulman and Brown nor Greenberg focused on a second type of drug approval included in Subpart H – codified now at 21 C.F.R. § 314.520.⁶⁰ This second avenue for Subpart H approval is reserved for circumstances in which “FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted.”⁶¹ Pursuant to this provision “FDA may approve a treatment subject to special

⁵⁷ See Thompson, *infra* Appendix A, at 170.

⁵⁸ Thompson, *infra* Appendix A, at 170.

⁵⁹ This codification was part of Congress’s major reauthorization and modernization of the Federal Food, Drug & Cosmetic Act. Section 506(b) of FDAMA (21 U.S.C. § 356) “in effect, codifie[d] in statute FDA’s Accelerated Approval Rule . . . , made final in 1992, which allows expedited marketing of certain new drugs or biological products intended to treat serious or life-threatening illnesses and that appear to provide meaningful therapeutic benefits to patients compared with existing treatments.” FDA Centers for Drug Evaluation and Research and for Biologics Evaluation and Research, *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*, at 2 (Sept. 1998) (footnote omitted). While clearly codifying Subpart H’s surrogate endpoint provision at 21 U.S.C. § 356(b)(1), Congress does not appear to have enacted a parallel provision to Section 314.520, which pertains to “restricted use” drugs, under which Mifeprex was approved.

⁶⁰ Section 314.520 (Approval with restrictions to ensure safe use.) states:

- (a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, such as:
 - (1) Distribution restricted to certain facilities or physicians with special training or experience; or
 - (2) Distribution conditioned on the performance of specified medical procedures.
- (b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

⁶¹ *Subpart H Final Rule*, 57 Fed. Reg. at 58942.

distribution or use restrictions that address outstanding safety issues.”⁶² Section 314.520 balanced FDA’s desire to bring clinically beneficial drugs to the market with the agency’s concern that “[s]ome drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use.”⁶³ The agency explained “that some clinically
 5 beneficial drugs can be used safely only if distribution and use are modified and restricted.”⁶⁴

Section 314.520 is intended for drugs that are vitally necessary, but which may impose greater than normal risks for the patient.⁶⁵ FDA was willing “to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to counterbalance the known safety concerns.”⁶⁶ Postmarketing restrictions would be designed “to
 10 enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction.”⁶⁷ FDA intended to employ restrictions on distribution “only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will *not* assure the product’s safe use.”⁶⁸ In the absence of restrictions, which “may vary with the circumstances of each drug[,] . . . the drug would be adulterated under Section 501
 15 of the act, misbranded under Section 502 of the act, or not shown to be safe under Section 505 of the act.”⁶⁹ In short, “[w]ithout such restrictions, the drugs would not meet the statutory criteria,

⁶² Geoffrey M. Levitt, James N. Czaban, and Andrea S. Paterson, “Chapter 6: Human Drug Regulation” in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 200.

⁶³ *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

⁶⁴ *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

⁶⁵ Of course, “[v]irtually all drug[s] can be toxic to humans, and no drug is completely free of risk,” but, as the seriousness of an illness and the effect of the drug on that illness increase, “the greater the acceptable risk from the drug.” *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

⁶⁶ *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

⁶⁷ *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

⁶⁸ *Subpart H Final Rule*, 57 Fed. Reg. at 58952 (emphasis added).

⁶⁹ *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

could not be approved for distribution, and would not be available for prescribing or dispensing.”⁷⁰ Mifeprex was the third of four drugs approved pursuant to Section 314.520.⁷¹

D. FDA’S APPROVAL OF MIFEPREX UNDER ITS ACCELERATED APPROVAL REGULATIONS (SUBPART H) WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

FDA’s accelerated approval regulations (Subpart H) apply to certain new drug products

“that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)”⁷² When it proposed Subpart H in 1992, FDA observed that the following types of illness would fall within the reach of Subpart H:

The terms “serious” and “life-threatening” would be used as FDA has defined them in the past. The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer’s dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel disease,

⁷⁰ *Subpart H Final Rule*, 57 Fed. Reg. at 58951. The agency continued: “The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing.” *Id.* at 58951-52.

⁷¹ On June 7, 2002, the drug Lotronex (alosetron hydrochloride) was reintroduced to the market after a *Supplemental NDA* was approved pursuant to Subpart H’s restricted distribution provision. See Letter, FDA/CDER, Florence Houn, M.D., Director, Office of Drug Evaluation III to Olivia Pinkett, Product Director, Regulatory Affairs, GlaxoSmithKline (June 7, 2002): at 1 (“This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program. . . . You have indicated your agreement with approval under restricted conditions.”).

⁷² 21 C.F.R. § 314.500. The rule was amended in 1999 to remove the words “and antibiotic.” See *Conforming Regulations Regarding Removal of Section 507 of the Federal Food, Drug, and Cosmetic Act, Final Rule*, 64 Fed. Reg. 396, 402 (Jan. 5, 1999).

asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, psychoses, and many other diseases can be serious for certain populations or in some or all of their phases.⁷³

5 According to FDA, the agency has approved 38 NDAs, including the Mifeprex application, under Subpart H.⁷⁴ Of these approvals, 20 were for the treatment of HIV and HIV-related diseases, nine were for the treatment of various cancers and their symptoms, four were for severe bacterial infections, one was for erythema nodosum leprosum (leprosy), one was for hypotension, and, finally, one was for the termination of unwanted pregnancies.⁷⁵

10 Pregnancy, without major complications, is not a “serious or life-threatening illness” for purposes of Subpart H. It is, rather, a normal physiological state experienced by most females one or more times during their childbearing years, and it is rarely accompanied by complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability. Thus, pregnancy is not the kind of exceptional circumstance
15 that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point.

⁷³ *Subpart H Proposed Rule*, 57 Fed. Reg. at 13235. In the *Subpart H Final Rule*, FDA asserted that “serious and life-threatening illnesses” would be readily identifiable: “FDA discussed the meaning of the terms ‘serious’ and ‘life-threatening’ in its final rules on ‘treatment IND’s’ (52 FR 19466 at 19467, May 22, 1987) and ‘subpart E’ procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every ‘serious’ and ‘life-threatening’ disease that would be within the scope of this rule. In FDA’s experience with ‘treatment IND’s’ and drugs covered by the ‘subpart E’ procedures there have not been problems in determining which diseases fall within the meaning of the terms ‘serious’ and ‘life-threatening,’ and FDA would expect no problems under this accelerated approval program.” *Subpart H Final Rule*, 57 Fed. Reg. at 58945.

⁷⁴ These estimates are based on the version of FDA’s webpage, dated February 5, 2002, listing Subpart H approvals, *infra* Appendix A.

⁷⁵ See FDA/CDER webpage, “NDAs Approved under Subpart H,” *infra* Appendix A. A copy of the most recently available version is reproduced in Appendix C (available at: <<http://www.fda.gov/cder/rdmt/accapp.htm>>). See also “NDA Supplements Approved under Subpart H” (available at: <<http://www.fda.gov/cder/rdmt/accapr1.htm>>) (supplemental approvals are not included in the figures set forth in the text because they refer to FDA actions regarding drugs that have already been approved).

In fact, the Population Council argued strenuously that its application for mifepristone did not fall within the scope of Subpart H.⁷⁶ In a letter to FDA written approximately three weeks before the final approval of the mifepristone NDA, the Population Council's Sandra P. Arnold protested, "... it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."⁷⁷ Arnold argued correctly that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."⁷⁸ She continued, stating, "Neither is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."⁷⁹ In the next paragraph, after directly quoting the *Subpart H Final Rule*, Ms. Arnold asserted that "[t]he plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."⁸⁰ She added that, unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."⁸¹ She continued that, "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."⁸²

⁷⁶ The Population Council appears to have been concerned about getting the drug approved "without invoking the Subpart H regulatory provisions that signal 'big deal' to the pharmaceutical industry." Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 4 [FDA FOIA Release: MIF 001333-49] ("Sandra Arnold Letter"). Sandra Arnold was "Vice President, Corporate Affairs" of the Population Council.

⁷⁷ Sandra Arnold Letter at 1.

⁷⁸ Sandra Arnold Letter at 1-2.

⁷⁹ Sandra Arnold Letter at 2.

⁸⁰ Sandra Arnold Letter at 2.

⁸¹ Sandra Arnold Letter at 2.

⁸² Sandra Arnold Letter at 2. Ms. Arnold also warned the agency that extending the scope of Subpart H to include pregnancy and unwanted pregnancy by exercising agency "judgment" was not defensible; the exercise of such judgment should go to whether or not "a particular disease actually is serious, not [act as] a means of stretching the meaning of serious to cover entirely new categories of non-serious situations." *Id.*

Additionally, Mifeprex fails to meet the second requirement set forth in Section 314.500 that drugs approved under Subpart H “provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)” As was noted above, the

5 Mifeprex Approval Memo contends “that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H [and] [t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure.”⁸³ By defining the “therapeutic benefit” solely as the avoidance of the current standard of care’s delivery mechanism, FDA effectively guarantees that a drug will satisfy this second prong of Subpart H as long as it

10 represents a different method of therapy.⁸⁴ It does not appear that such considerations formed the basis of any other Subpart H approval.

When FDA adopted Subpart H, it cited as “readily understood illustrations of the intent of the [meaningful therapeutic benefit] requirement” an “improved response compared to available therapy” and the “ability to treat unresponsive or intolerant patients.”⁸⁵ Based on these

15 illustrations, Mifeprex does not fall within the intent of the requirement. First, there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions. Dr. Jeffrey Jensen conducted a study to compare the safety and

⁸³ Mifeprex Approval Memo at 6.

⁸⁴ The view that merely making a different mode of therapy available *per se* produces a benefit is inconsistent with the position the agency has articulated elsewhere. MAPP 6020.3, which defines eligibility for FDA priority review, suggests that drug therapies are not inherently superior to non-drug therapies. Specifically, a drug may be afforded priority review if it would provide a significant improvement when compared with “marketed products . . . including non-“drug” products/therapies.” See FDA/CDER, “Review Management: Priority Review Policy,” MAPP 6020.3, at 1 (Apr. 22, 1996).

⁸⁵ *Subpart H Final Rule*, 57 Fed. Reg. at 58947.

efficacy of medical abortion with that of surgical abortion.⁸⁶ The study compared 178 patients who, as participants in the U.S. clinical trial in support of the Mifeprex NDA, underwent mifepristone/misoprostol abortions, with 199 patients who later received surgical abortions at the same clinical site. The primary procedure failed (*i.e.*, there was a subsequent surgical intervention) in 18.3 percent of the mifepristone/misoprostol patients and 4.7 percent of the surgical patients.⁸⁷ Of the mifepristone/misoprostol patients who failed their primary procedure, 12.5 percent required surgical intervention for acute bleeding, 43.8 percent for persistent bleeding, 15.6 percent for incomplete abortion, and 28.1 percent for ongoing pregnancy.⁸⁸ By contrast, the sole cause for surgical intervention among the surgical patients who failed their primary procedure was persistent bleeding.⁸⁹ In addition, mifepristone/misoprostol patients “reported significantly longer bleeding” and “significantly higher levels of pain . . . , nausea . . . , vomiting . . . , and diarrhea” than their surgical counterparts.⁹⁰

Second, Mifeprex does not treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion. To the contrary, because “medical abortion failures should be managed with surgical termination” the option for surgical abortion must be available for any Mifeprex patient.⁹¹ As the U.S. trial conducted in support of the NDA indicated, the possibility

⁸⁶ Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, “Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study,” *Contraception* 59 (1999): 153-159 (“Jensen Study”)[FDA FOIA Release: MIF 000438-44].

⁸⁷ See Jensen Study, *infra* Appendix A, at 155, Table 2.

⁸⁸ See Jensen Study, *infra* Appendix A, at 156, Table 3.

⁸⁹ See Jensen Study, *infra* Appendix A, at 156, Table 3.

⁹⁰ Jensen Study, *infra* Appendix A, at 156.

⁹¹ Mifeprex Label (“Warnings”).

for failure is substantial.⁹² Thus, any patient who would be intolerant of surgical abortion, if such a class of patients exists, cannot use the Mifeprex Regimen.

As discussed below, FDA approved Mifeprex pursuant to Section 314.520 in order to impose safety restrictions to counteract the risks it had identified. FDA, confronted by the sponsor's refusal to establish voluntary restrictions on distribution,⁹³ viewed Subpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe.⁹⁴ The inappropriate application of Section 314.520 served the agency's immediate need of conditioning the drug's approval on certain safety measures. However, Mifeprex fails to satisfy the Subpart H requirements because, although it presents great risk to the user, it neither treats a serious or life-threatening illness nor provides a therapeutic benefit above existing treatments. A drug with such characteristics should not have been approved.

⁹² FDA, "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments," at 11 (Table 1) (reporting a failure rate of 8% for pregnancies less than or equal to 49 days' duration) ("Medical Officer's Review").

⁹³ Early in the approval process, FDA anticipated that the Population Council would cooperate, thus obviating the need for Subpart H restrictions: "[B]ecause the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted." See Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62]. The voluntary restrictions placed on the drug Accutane, a drug for severe acne, illustrate that a cooperative drug sponsor may be able to obviate the need for Subpart H restrictions. Because Accutane can cause birth defects, the restrictions are designed to ensure that women taking the drug are not and do not become pregnant. The "System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™)," controls the distribution of the drug through the issuance of yellow Accutane Qualification Stickers. These stickers are distributed to physicians who meet a number of qualifications and they, in turn, distribute them to patients, who must undergo two tests to confirm they are not pregnant and must commit to use two forms of contraception. Pharmacists may fill prescriptions for the drug only if they bear the qualification sticker, were issued within the past week, and prescribe no more than 30 days' worth of the drug. See Accutane Label.

⁹⁴ This interpretation of the agency's actions is supported by FDA spokeswoman Crystal Rice, who said "that outside of Subpart H, the FDA does not have another regulatory program to mandate safety restrictions on drug marketing for drugs used to treat 'serious or life-threatening illnesses'" and "that 'other agreements [or restrictions on the drug] not under Subpart H worked out between FDA and a sponsor would be essentially voluntary.'" "Danco Medical Director Explains Mifepristone's FDA Approval Not Fast-Track or Accelerated, Despite Media Reports," *Kaiser Daily Reproductive Health Report* (March 29, 2001) (available at: <<http://report.kff.org/archive/repro/2001/3/kr010329.5.htm>>).

E. THE CLINICAL TRIALS DID NOT PRESENT “SUBSTANTIAL EVIDENCE” THAT THE MIFEPREX REGIMEN IS SAFE AND EFFECTIVE

FDA’s approval of the Mifeprex NDA ran counter to Congress’s statutory requirements, the agency’s regulations and guidance documents, and FDA’s well-established standards for the quality and quantity of scientific evidence needed to support an agency finding that a new drug is safe and effective. The clinical trials submitted by the Population Council to support its NDA did not use the full set of design features FDA typically requires to produce unbiased investigations of drug safety and effectiveness. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex Regimen. Inexplicably, FDA failed to perform a statistical analysis of the data from the American trial. Furthermore, FDA’s approval of Mifeprex pursuant to Subpart H compounds the deficiencies in the trials because sponsors of Subpart H drugs must demonstrate that the drug for which approval is being sought provides a “meaningful therapeutic benefit over existing therapy.” Because Mifeprex was approved in reliance on French and American trials that did not compare the Mifeprex Regimen with the existing standard of care for ending pregnancies (*i.e.*, surgical abortion), the trials cannot support this Subpart H approval.

1. The Clinical Trials Underlying FDA’s Approval of Mifeprex

FDA based its approval of Mifeprex on safety and effectiveness data derived from two French clinical trials (“French Clinical Trials”) and one U.S. clinical trial (“U.S. Clinical Trial”).⁹⁵ Neither the French Clinical Trials nor the U.S. Clinical Trial was blinded, randomized,

⁹⁵ See Mifeprex Approval Memo, *infra* Appendix A, at 1.

or concurrently controlled – the hallmarks of unbiased, scientific analysis generally relied upon by FDA.

a. The French Clinical Trials

5 The French Clinical Trials, which formed the basis for the Population Council's original NDA submission in 1996, were open-label, multi-center studies.⁹⁶ One of these trials consisted of 1,286 patients at 24 centers in France ("French Trial I").⁹⁷ The trial was limited to women who had pregnancies of no more than 49 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.⁹⁸ On the first day of the procedure, the patient received
10 600 mg of mifepristone orally "in the presence of a study investigator."⁹⁹ Approximately 48 hours later, she returned and, unless the abortion had already taken place, ingested 400 micrograms of misoprostol "in the presence of a study investigator."¹⁰⁰ The patient remained under observation for four hours or more after the ingestion of misoprostol and returned for "a final assessment of the pregnancy termination procedure" eight to 15 days later.¹⁰¹

⁹⁶ FDA's Reproductive Health Drugs Advisory Committee ("FDA Advisory Committee"), which met in July 1996 to consider the mifepristone NDA, based its conclusion primarily on the French trial along with preliminary data from the U.S. Clinical Trial. See FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 6, 132-33 (July 19, 1996) (FDA Hearings Transcript) [FDA FOIA Release: MIF 005200-90]. Committee member Dr. Mary Jo O'Sullivan asked why the Committee meeting was being held "at this time when the data is not finalized." *Id.* at 37. Dr. C. Wayne Bardin, who was responsible for overseeing the Population Council's NDA preparation, responded that "we have sufficient data . . . [f]rom the non-U.S. data to allow us to submit an application to the FDA." *Id.*

⁹⁷ See FDA, Statistical Review and Evaluation, at 2-4 (May 21, 1996) ("Statistical Review"). This French trial is referred to as FFR/91/486/14.

⁹⁸ See Statistical Review, *infra* Appendix A, at 2. "Since the ultrasound estimate of gestational age was more reliable than the patient's estimate . . . gestational age based on the ultrasound examination was used if available." *Id.* Investigators, in violation of study protocol, included some women with pregnancies of more than 49 days. See Statistical Review, *infra* Appendix A, at 3.

⁹⁹ See Statistical Review, *infra* Appendix A, at 2.

¹⁰⁰ See Statistical Review, *infra* Appendix A, at 2.

¹⁰¹ See Statistical Review, *infra* Appendix A, at 2.

The efficacy analysis of French Trial I encompassed only 1,205 patients, while the safety analysis included all 1,286 participants.¹⁰² The regimen resulted in “complete expulsion” in 95.4 percent of the 1,189 participants whose pregnancies were 49 days or less.¹⁰³ The rate of complete expulsion declined with increased gestational age.¹⁰⁴ Sixty-one women had complete expulsions before taking misoprostol.¹⁰⁵ Almost 86 percent of patients in French Trial I experienced at least one adverse event as a result of the procedure.¹⁰⁶

The second French clinical trial (“French Trial II”) enrolled 1,194 patients at 11 centers.¹⁰⁷ The trial was limited to women who had pregnancies of no more than 63 days’ gestational age, as established by ultrasound, if available, or by the patient’s estimate.¹⁰⁸ The regimen used in French Study II was essentially the same as that described above in connection with French Study I, except that an additional 200 micrograms of misoprostol was administered if complete expulsion did not occur within three hours after taking the initial 400 microgram dose of misoprostol.¹⁰⁹ Patients who received the second dose of misoprostol remained under observation for a total of five hours.¹¹⁰

¹⁰² See Statistical Review, *infra* Appendix A, at 3.

¹⁰³ See Statistical Review, *infra* Appendix A, at 3. Patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (2.8%), ongoing pregnancies (1.5%), and those who needed surgical procedures for bleeding (.3%) were classified as failures. See *id.* at 3 and 9 (Table 1).

¹⁰⁴ See Statistical Review, *infra* Appendix A, at 3 (“[T]here was a statistically significant . . . inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.”).

¹⁰⁵ See Statistical Review, *infra* Appendix A, at 3. Twenty-six of these women received misoprostol anyway, because the investigators did not realize that they had had complete abortions. See *id.*

¹⁰⁶ See Statistical Review, *infra* Appendix A, at 4.

¹⁰⁷ See Statistical Review, *infra* Appendix A, at 4-7. This French trial is designated as FF/92/486/24.

¹⁰⁸ See Statistical Review, *infra* Appendix A, at 4-5.

¹⁰⁹ See Statistical Review, *infra* Appendix A, at 5.

¹¹⁰ See Statistical Review, *infra* Appendix A, at 5.

The efficacy analysis of French Trial II encompassed only 1,104 patients, while the safety analysis included all 1,194 participants.¹¹¹ The regimen resulted in “complete expulsion” in 92.8 percent of the participants.¹¹² The rate of complete expulsion declined with increased gestational age.¹¹³ Twenty-six women had complete expulsions before taking misoprostol.¹¹⁴

5 Almost 93 percent of patients in French Trial II experienced at least one adverse event as a result of the procedure.¹¹⁵

Among the deficiencies that characterized both French Clinical Trials was the absence of an appropriate control group. Consequently, as an FDA statistician concluded after reviewing the data from the French Clinical Trials: “In the absence of a concurrent control group in each of
10 these studies, it is a matter of clinical judgment whether or not the sponsor’s proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy.”¹¹⁶

b. The U.S Clinical Trial

15 The U.S. Clinical Trial was carried out from September 13, 1994 to September 12, 1995 at various qualified university hospitals and clinics.¹¹⁷ Patients had to satisfy a number of criteria

¹¹¹ See Statistical Review, *infra* Appendix A, at 5.

¹¹² See Statistical Review, *infra* Appendix A, at 6. As in French Study I, patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (4.0%), ongoing pregnancies (2.3%), and those who needed surgical procedures for bleeding (.9%) were classified as failures. See *id.* at 5 and 12 (Table 4).

¹¹³ See Statistical Review, *infra* Appendix A, at 6.

¹¹⁴ See Statistical Review, *infra* Appendix A, at 6.

¹¹⁵ See Statistical Review, *infra* Appendix A, at 7.

¹¹⁶ Statistical Review, *infra* Appendix A, at 7-8.

¹¹⁷ See Medical Officer’s Review, *infra* Appendix A, at 6. More specifically, the U.S. Clinical Trial consisted of “two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols.” Medical Officer’s Review, *infra* Appendix A, at 6 and 9. In this Petition, the trials will be referred to as “the U.S. Clinical Trial,” because the protocols employed were identical, the results of the two trials were analyzed jointly, and the results were published in the same article. See Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri

to be included in the study.¹¹⁸ All patients were screened by pelvic examination and ultrasound to ensure that their pregnancies were not too advanced for the procedure.¹¹⁹ On their first visit, patients took 200 mg of mifepristone orally “[i]n the presence of the investigator.”¹²⁰ Patients returned 36 to 60 hours later to ingest 400 micrograms of misoprostol orally in the presence of the investigator, unless the investigator determined that the termination was already complete.¹²¹ Following ingestion of misoprostol, patients were observed for a minimum of four hours.¹²² Patients were instructed to return again 12 days later for a follow-up assessment.¹²³ A patient’s pregnancy was terminated surgically “at any time if the investigator believed there was a threat to a woman’s health (medically indicated), at a woman’s request, or at the end of the study for an ongoing pregnancy or incomplete abortion.”¹²⁴

Benton, M.D., and Ann Robbins, “Early Pregnancy Termination with Mifepristone and Misoprostol in the United States,” *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 (“Spitz Article”) [FDA FOIA Release: MIF 006692-97]. The members of the FDA Advisory Committee who were still working for FDA at the time of publication received a copy of the Spitz Article. See Medical Officer’s Review, *infra* Appendix A, at 29. Although FDA considered data from the entire U.S. Clinical Trial, it appears that the agency formally approved Mifeprex based only on the portion of the U.S. Clinical Trial data that was generated among women whose pregnancies were no more than 49 days’ gestational age. See Mifeprex Approval Memo, *infra* Appendix A, at 1 (“The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period.”). See also Mifeprex Label (“Clinical Studies”).

¹¹⁸ Among the inclusion criteria were requirements that a patient be at least 18 years old, be in good health, have an intrauterine pregnancy of no more than 63 days (confirmed by a pelvic examination *and* ultrasound), and have agreed to a surgical abortion if the mifepristone-misoprostol abortion failed. Medical Officer’s Review, *infra* Appendix A, at 7-8. The study excluded women with certain health problems, such as liver, respiratory, or renal disease, cardiovascular disease, chronic hypertension, anemia, clotting problems, pelvic inflammatory disease, and ectopic pregnancies. See *id.* at 8. In addition, women who were over 35 and smoked, had IUDs, were breastfeeding, were unlikely to comply with study requirements, or who “[l]ived or worked more than one hour from the emergency care facility” were excluded. See *id.* at 8-9.

¹¹⁹ See Medical Officer’s Review, *infra* Appendix A, at 8.

¹²⁰ Medical Officer’s Review, *infra* Appendix A, at 9.

¹²¹ See Medical Officer’s Review, *infra* Appendix A, at 9.

¹²² See Medical Officer’s Review, *infra* Appendix A, at 7.

¹²³ See Medical Officer’s Review, *infra* Appendix A, at 7.

¹²⁴ Medical Officer’s Review, *infra* Appendix A, at 16.

The U.S. Clinical Trial consisted of 2,121 subjects.¹²⁵ Of these patients, 2,015 were evaluated for efficacy,¹²⁶ which “was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure.”¹²⁷ The remaining 106 patients did not return for the third visit.¹²⁸ The mifepristone-misoprostol combination was effective in 92 percent of patients with pregnancies no greater than 49 days, 83 percent of patients with pregnancies between 50 and 56 days, and 77 percent of women with pregnancies between 57 and 63 days.¹²⁹ All 2,121 subjects were evaluated for safety.¹³⁰ Ninety-nine percent of patients experienced adverse events and most of these experienced multiple adverse events.¹³¹ Twenty-three percent of the adverse effects experienced by each gestational age group were “severe.”¹³²

Finally, FDA did not conduct a statistical review of the results of the U.S. Clinical Trial. FDA’s statistical reviewer explained this failure by noting that “[a] statistical evaluation of the European studies was completed previously ”and “[t]he clinical results of the supporting U.S.

¹²⁵ See Medical Officer’s Review, *infra* Appendix A, at 10.

¹²⁶ See Medical Officer’s Review, *infra* Appendix A, at 10.

¹²⁷ Medical Officer’s Review, *infra* Appendix A, at 16. The failure to establish a pre-trial, statistical definition for drug efficacy was a defect in trial design.

¹²⁸ See Medical Officer’s Review, *infra* Appendix A, at 16. It would have been appropriate to include these 106 patients in the efficacy analysis as “failures,” if for no other reason than that they did not appear for all three required visits. Although “[f]or 92 of these patients, there was some information suggesting a successful outcome,” *id.* at 10, there was neither definitive evidence of complete abortion nor, apparently, any information with respect to whether these women subsequently experienced any adverse effects. In fact, during their second visit, five of these 106 women were diagnosed as having continuing pregnancies. *Id.* at 10. See also Spitz Article, *infra* Appendix A, at 1246 (“The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women.”).

¹²⁹ See Medical Officer’s Review, *infra* Appendix A, at 11 (Table 1).

¹³⁰ See Medical Officer’s Review, *infra* Appendix A, at 10.

¹³¹ See Medical Officer’s Review, *infra* Appendix A, at 11.

¹³² See Medical Officer’s Review, *infra* Appendix A, at 11.

studies . . . are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required.”¹³³

2. Requirements for Proving Drug Safety and Effectiveness

FDA has developed a rigorous default standard for scientific demonstrations of safety and effectiveness of human drug products.¹³⁴ Section 505(d)(5) of the FD & C Act provides, in relevant part, that FDA shall refuse to approve a new drug application when “there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”¹³⁵ Section 505(d) defines “substantial evidence” to mean “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved”¹³⁶ FDA has stated that “substantial evidence” requires a showing of clinically significant evidence of effectiveness rather than mere statistical evidence of significance.¹³⁷ No such showing was made for Mifeprex, which has been demonstrated to be less effective than surgical abortion for all segments of the population.

¹³³ FDA, “Statistical Comments on Amendment 024,” Memorandum to File NDA 20-687 (Feb. 14, 2000). This document is available along with the agency’s Statistical Review. *See* Statistical Review, *infra* Appendix A.

¹³⁴ *See* the discussion of the development and requirements of FDA’s “gold standard,” *supra* Section III.C.1.

¹³⁵ 21 U.S.C. § 355(d)(5).

¹³⁶ 21 U.S.C. § 355(d) (“the term ‘substantial evidence’ means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”).

¹³⁷ *See Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 155 (D.C. Cir. 1986) (“It is important to note that the Commissioner does not contend that the effectiveness shown must amount to a ‘medical breakthrough’, as ARW complains, but contends in his brief that he would be satisfied with even a modest clinical or therapeutic effect.”).

Section 314.126 of FDA's rules states that "[r]eports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."¹³⁸ The rule states that a major purpose of an adequate and well-designed study is to "permit[] a valid comparison with a control to provide a quantitative assessment of drug effect."¹³⁹ According to Section 314.126(b), an adequate and well-controlled study serves to ensure that the subjects of the trial have the disease or condition being studied,¹⁴⁰ that the method of assigning patients to treatment and control groups minimizes bias (e.g., using randomization),¹⁴¹ and, that "[a]dequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data" (e.g., blinding).¹⁴² The criteria that the rule establishes "have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation."¹⁴³

Agency guidance provides that FDA may approve an NDA based on only one, not two, effectiveness trials for drugs in one of the following three categories:

- 1) when effectiveness may be demonstrated adequately with existing studies of another claim or dose (e.g., approval for pediatric use on the basis of studies in adults); 2) when a controlled trial of a specific new use is supported by evidence from adequately controlled trials from related uses, dosages, or endpoints; and 3) when a single multicenter trial provides statistically convincing and clinically meaningful evidence of effectiveness, supported by confirmatory research.¹⁴⁴

¹³⁸ 21 C.F.R. § 314.126(a) ("Adequate and well-controlled studies.").

¹³⁹ 21 C.F.R. § 314.126(b)(2) (describing "placebo concurrent control," "dose-comparison concurrent control," "no treatment concurrent control," "active treatment concurrent control," and "historical control").

¹⁴⁰ 21 C.F.R. § 314.126(b)(3).

¹⁴¹ 21 C.F.R. § 314.126(b)(4).

¹⁴² 21 C.F.R. § 314.126(b)(5).

¹⁴³ 21 C.F.R. § 314.126(a).

¹⁴⁴ Kulynych, *infra* Appendix A, at 146 (citing FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) at 5-17 (*FDA Effectiveness Guidance*)).

Mifepristone did not fall within any of these categories. The first and second categories were inapposite because mifepristone had not been approved for any use in any population in the United States; additionally, no evidence from adequate and well-controlled trials had ever been presented to FDA regarding any use for mifepristone. Because neither the French Clinical Trials nor the U.S. Clinical Trial was randomized, blinded,¹⁴⁵ or comparator-controlled, none of these trials could provide the type of data necessary for the third category either. Furthermore, these studies lacked “clear, prospectively determined clinical and statistical analytic criteria.”¹⁴⁶

Even though FDA takes the position elsewhere that the extent to which a trial’s design controls for various types of bias “is a critical determinant of its quality and persuasiveness,”¹⁴⁷ neither the French Clinical Trials nor the U.S. Clinical Trial were randomized, concurrently controlled, or blinded. A control group “allow[s for] discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment.”¹⁴⁸ Control groups also enable investigators to

¹⁴⁵ Blinding is the normal method by which those who evaluate a medication’s effectiveness and side effects, are kept unaware of whether they are evaluating the comparator drug (sometimes a placebo), or the new medication (or procedure) under study. If possible, the patient is also blinded and not allowed to know which treatment she is receiving (“double-blinding”). According to standard scientific and medical practice and the standards to which FDA holds pharmaceutical sponsors, all clinical research studies investigating the effects of new drugs should be subjected to an assessment by a blinded evaluator. Conducting a concurrently-controlled, randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable. There are study designs that would have also allowed for blinding. Had blinding proved too difficult to perform, the requirement could have been waived based upon a satisfactory showing by the sponsor.

¹⁴⁶ *FDA Effectiveness Guidance, infra* Appendix A, at 12.

¹⁴⁷ FDA, “Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials,” (Rockville, Md.: May 2001) at 3 (§ 1.2.1) (*FDA Guidance (ICH: E10): Choice of Control Group*). FDA’s publication of “E10” is available at: <<http://www.fda.gov/cder/guidance/4155fml.pdf>>.

¹⁴⁸ *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2) (Introduction, “Purpose of Control Group”).

determine “what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective.”¹⁴⁹

A trial that employs a concurrent control group drawn from the same population yields the most robust data. Concurrent control groups are chosen from the same population as the test group and are “treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time.”¹⁵⁰ When concurrent control groups are used, the treatment and non-treatment groups are similar in all baseline and non-treatment variables that could influence the outcome or introduce bias into the study.¹⁵¹

By contrast, in a trial using external or historical controls “the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group.”¹⁵² FDA cautions:

“The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome). Use of the latter comparator is particularly treacherous (such trials are usually considered uncontrolled) because general impressions are so often inaccurate.”¹⁵³

In such a trial, “[t]he control group is thus not derived from exactly the same population as the treated population.”¹⁵⁴ If, as is most common, the external control group is composed of “a well-documented population of patients observed at an earlier time,” the trial is said to be

¹⁴⁹ FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 3 (§ 1.2).

¹⁵⁰ FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 3 (§ 1.2).

¹⁵¹ See FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 3 (§ 1.2). “Bias here . . . means the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value.” *Id.*

¹⁵² FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 26 (§ 2.5.1).

¹⁵³ FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 5 (§ 1.3.5).

¹⁵⁴ FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 26 (§ 2.5.1).

“historically” controlled.¹⁵⁵ Blinding and randomization are also not available to minimize bias when external or historical controls are used.¹⁵⁶

According to FDA, the “[i]nability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable.”¹⁵⁷ A legal commentator recently cautioned courts about the scientific validity of experiments and trials that have no concurrent control.¹⁵⁸ She explained that “historically controlled subjects have not been subjected to exactly the same conditions as the test subjects.”¹⁵⁹ Consequently, “one must be wary of” non-concurrently controlled studies (*i.e.*, historical, external, or uncontrolled studies) because their conclusions can be manipulated more easily than if concurrent controls are used.¹⁶⁰

3. FDA’s Acceptance of the French and U.S. Clinical Trial Data Violated Section 314.126(e) of the Agency’s Rules

Section 314.126(e) of FDA’s rules states unequivocally that “[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness.”¹⁶¹ The section authorizes the use of uncontrolled trials merely to present supporting evidence for controlled trials; uncontrolled trials, if they are “carefully conducted and

¹⁵⁵ See FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 26 (§ 2.5.1) (“but it could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study.”).

¹⁵⁶ FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 27 (§ 2.5.2).

¹⁵⁷ FDA Guidance (ICH: E10): Choice of Control Group, *infra* Appendix A, at 26 (§ 2.5.2).

¹⁵⁸ Erica Beecher-Monas, “The Heuristics of Intellectual Due Process: A Primer for Triers of Science,” *New York University Law Review* 75: 1563-1657, 1628.

¹⁵⁹ Beecher-Monas, *infra* Appendix A, at 1628, n.357.

¹⁶⁰ Beecher-Monas, *infra* Appendix A, at 1628, n.357 (“‘you can prove anything with selective controls,’ so one must be wary of historical controls,” Beecher-Monas quoting Jon Cohen, “Cancer Vaccines Get a Shot in the Arm,” 262 *Science* 841, 843 (1993)).

¹⁶¹ 21 C.F.R. § 314.126(e)(emphasis added).

documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug.”¹⁶²

FDA recognizes a limited role for external, historically controlled studies. The agency takes the position that “[h]istorical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference.”¹⁶³ Similarly, Section 314.126 cautions that “[b]ecause historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent controlled populations, historical control designs are usually reserved for special circumstances.”¹⁶⁴ FDA cites as an example, “studies of diseases with high and predictable mortality (for example, certain malignancies),”¹⁶⁵ in which a decision might be made to offer all trial participants a potentially effective drug. Externally controlled studies also may suffice because “the effect of the drug is self-evident (general anesthetics, drug metabolism).”¹⁶⁶

The French and U.S. Clinical Trials, which did not employ either external or historical control groups, were uncontrolled. During the Advisory Committee Hearings, FDA’s Dr.

Ridgley C. Bennett, who summarized the data from the French Clinical Trials, stated:

There are very few studies comparing medical methods and vacuum aspiration for termination of early pregnancy. To date, no large randomized controlled trials have compared mifepristone plus misoprostol with suction curettage abortion. However, large published series have demonstrated morbidity rates associated with mifepristone plus prostaglandin to be similar to those of suction-curettage.¹⁶⁷

¹⁶² 21 C.F.R. § 314.126(e).

¹⁶³ *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.2.2.2). According to FDA guidance, the “main advantage” of an externally controlled trial “is that all patients can receive a promising drug, making the study more attractive to patients and physicians.” *FDA Guidance (ICH: E10): Choice of Control Group*, *infra* Appendix A, at 27 (§ 2.5.6).

¹⁶⁴ 21 C.F.R. § 314.126(b)(2)(v) (“Historical control.”).

¹⁶⁵ 21 C.F.R. § 314.126(b)(2)(v).

¹⁶⁶ 21 C.F.R. § 314.126(b)(2)(v).

¹⁶⁷ FDA Hearings Transcript, *infra* Appendix A, at 130. Jensen and his fellow researchers conducted “[a] prospective, noncurrent, single center cohort comparison.” See Jensen Study, *infra* Appendix A, at 153. The study

“Published series” and uncontrolled studies cannot serve as a substitute for the well-controlled clinical trials that FDA requires. A concurrent control group would have been feasible because the trial participants were prepared to receive surgical abortion in the event of a failed
 5 mifepristone abortion.

The unusual circumstances that sometimes justify relying on externally controlled trials are not applicable with respect to pregnancy termination, generally, or the termination using mifepristone and misoprostol, specifically. Randomized, concurrently-controlled, blinded trials would have allowed investigators to compare not only the relative rates of complete termination
 10 and expulsion, but also the nature, intensity, and duration of the numerous side effects. In the absence of concurrent controls and blinding, the duration and intensity of cramping, nausea, bleeding, pain, and any emotional or psychological effects of the treatments would be subject to investigator and patient bias. The design of the U.S. Clinical Trial precluded unbiased comparison groups that could have helped analysts arrive “at a complete understanding of
 15 potential advantages, disadvantages and differences” between medical and surgical abortion.¹⁶⁸

FDA’s *de facto* waiver of Section 314.126(e) constituted a gross departure from its past practice and announced standards for the conduct of adequate and well-controlled clinical trials.¹⁶⁹

compared the data from Mifeprex patients at one of the sites that participated in the U.S. Clinical Trial with data from patients who subsequently underwent surgical abortions at the same site. Although the methodological quality of this study is arguably superior to either the French or U.S. Clinical Trials, had it been offered as trial data it also would have been a weak substitute for a randomized controlled trial establishing equivalent or superior efficacy to surgical abortion.

¹⁶⁸ See Jensen Study, *infra* Appendix A, at 156. Dr. Cassandra Henderson, a member of the FDA Advisory Committee, wondered about this point as well: “Since this regimen is not without any side effects and we know that spontaneous abortion is not an infrequent occurrence, is it appropriate to use historical controls in trying to evaluate the efficacy of this regimen and not a randomized placebo trial?” FDA Hearings Transcript, *infra* Appendix A, at 131 (FDA’s Dr. Ridgely C. Bennett gave the following puzzling response: “Well, I think it would be difficult to do a randomized trial of this nature. But I think it is fair to use a historical control for efficacy.”).

¹⁶⁹ There is no evidence that FDA formally issued a waiver under Section 314.126(c) of the requirement for well-controlled studies or that the Population Council ever requested such a waiver.

4. Subpart H's Standard for Proving Drug Effectiveness

The approval of a drug under Subpart H does not lower the applicable standards for proving the drug's effectiveness. As FDA stated when it adopted Subpart H, "[a]ll drugs approved [under Subpart H] will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."¹⁷⁰ In fact, Subpart H is available only for drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients *over existing treatments* (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."¹⁷¹ Neither the French nor the U.S. Clinical Trials yielded scientifically valid comparisons with the existing therapy, surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments." FDA should have required the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone has a meaningful therapeutic benefit over the standard method for terminating pregnancies. FDA did not require the drug sponsor to perform such trials for Mifeprex, which departs from FDA's normal treatment of Subpart H drugs generally and for the other drugs approved under the restricted distribution provisions in Section 314.520.

Mifeprex appears to be the only drug that FDA has approved under Section 314.520 of Subpart H without requiring compliance with the statutory and regulatory requirements that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials capable of providing data for subsection to rigorous statistical analysis.

¹⁷⁰ *Subpart H Final Rule*, 57 Fed. Reg. at 58953.

¹⁷¹ 21 C.F.R. § 314.500 (emphasis added). The class of "existing treatments" to which there must be a comparison, as specified in this rule section, is not limited to pharmaceuticals. For example, a potential chemotherapeutic agent might be compared to radiation therapy.

Aside from Mifeprex, only four drugs have been approved pursuant to Section 314.520, the restricted distribution prong of Subpart H. Each of these drugs, Xeloda,¹⁷² Thalomid,¹⁷³ Actiq,¹⁷⁴ and Tracleer,¹⁷⁵ was an appropriate candidate for approval under Section 314.520. Moreover, in each case, studies were performed that allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care. FDA's decision to require randomized, comparator-controlled, blinded trial design for each drug, even in the face of urgent need for the treatments at issue, supports the claim that FDA's treatment of the mifepristone NDA was aberrant.

Xeloda™ (capecitabine) was approved for use in treating patients with widely metastatic ("Stage IV") terminal breast cancer, for whom all other modalities of chemotherapy have failed or are contraindicated.¹⁷⁶ The average lifespan of a patient with multi-drug resistant tumors participating in the clinical trials for this drug was only 8.5 months. Because Xeloda was only modestly effective (25% of the recipients improved for an average of five months), exhibited significant toxicity, and was a last resort treatment for dying patients, FDA approved it under Section 314.520 with use restrictions and commitments to further study the drug. Subsequent randomized, concurrent controlled, blinded evaluator trials demonstrated Xeloda's statistical superiority to the standard of care for metastatic colon and breast cancers.¹⁷⁷

¹⁷² NDA 20896.

¹⁷³ NDA 20785.

¹⁷⁴ NDA 20747.

¹⁷⁵ NDA 21290.

¹⁷⁶ See "NDAs Approved under Subpart H," *infra* Appendix A. The current version of the Subpart H approval chart (updated Aug. 8, 2002) indicates that Xeloda is a "surrogate endpoint" drug, rather than a restricted distribution drug. However, the two previous postings of the chart state the opposite. Furthermore, FDA's approval letter states that the NDA "[was] approved under 21 CFR 314.520." Letter, FDA/CDER to Cynthia Dinella, Group Director, Regulatory Affairs, Hoffman-La Roche Inc. (Apr. 30, 1998).

¹⁷⁷ See Xeloda package insert.

Thalidomide (ThalomidTM) was approved under Section 314.520 for the treatment of leprosy, a disfiguring, chronically disabling, and often lethal skin infection.¹⁷⁸ Thalidomide is a drug the severe toxicity of which, particularly to fetuses, is well-documented. Children exposed to this drug *in utero* suffer dramatic birth defects, namely the partial absence of hands, feet, arms and legs. The public outcry following the discovery that thalidomide causes these alarming malformations helped to spur the scientific modernization of FDA drug approval policy and practices in the 1960s. Clinical trials involving leprosy are difficult and require long periods of time because the disease is very rare in the United States. Three randomized, double-blinded comparator-controlled clinical trials were performed to support the Thalomid NDA.¹⁷⁹

Oral fentanyl citrate (ActiqTM) was approved under Section 314.520 as a powerful sedating narcotic painkiller, primarily for use to relieve the suffering of dying cancer patients.¹⁸⁰

Actiq can be lethal, particularly to children, because it quickly abolishes a patient's drive to breathe, unless the patient is already accustomed to narcotic analgesics. Moreover, Actiq, a powerful narcotic, has a high potential for abuse and diversion into the illegal drug market.

Actiq was evaluated in a "double blinded, placebo controlled" study for the treatment of breakthrough cancer pain and was shown to "produce statistically significantly more pain relief compared with placebo."¹⁸¹ Actiq is restricted for use only by oncologists and pain specialists who are familiar with the management of the side effects and complications of the drug's use as approved.

¹⁷⁸ See "NDAs Approved under Subpart H," *infra* Appendix A.

¹⁷⁹ See Thalomid package insert.

¹⁸⁰ See "NDAs Approved under Subpart H," *infra* Appendix A.

¹⁸¹ Actiq package insert.

Tracleer™ (bosentan tablets) was approved pursuant to Section 314.520 for use in treating pulmonary hypertension, a life threatening and frequently progressive condition of excessively high blood pressure in the lung blood vessels resulting from chronic scarring and injury of the lung tissue.¹⁸² Tracleer can cause liver damage and major birth defects. Two
 5 randomized, double-blinded, placebo-controlled clinical trials demonstrated the superiority of the drug over a placebo. Tracleer was compared to a placebo because there is no alternate standard of care for pulmonary hypertension. Despite its potential toxicity, Tracleer was approved subject to usage restrictions under Section 314.520 because it is the only treatment available for a life threatening and debilitating condition.¹⁸³

10 5. FDA Failed to Require a Comprehensive Audit of French Clinical Trial Data after Discovering Violations of Good Clinical Practices

In June 1996, FDA inspected the trial records of a “French government-supported
 15 abortion clinic” that participated in the French Clinical Trials. FDA issued a Form 483 detailing problems uncovered during the inspection. The problems identified by the investigator suggested carelessness, fraud, evidence tampering, and the systematic under-reporting of serious adverse events. The inspection “revealed a failure to maintain complete and accurate records.” The violations that were discovered included: “laboratory reports that were missing” for 11
 20 patients, “missing ultrasound documents” for 20 patients, “pages missing from the case record files and unreported aspirations,” inclusion of 4 ineligible patients, and “consent forms were dated after the start of study for some subjects, and the investigator had signed consent form

¹⁸² See “NDAs Approved under Subpart H,” *infra* Appendix A.

¹⁸³ See Tracleer package insert.

sometimes in advance, up to 4 days before the subjects had signed.”¹⁸⁴ There were also “under-reported side effects” such as “a patient bleeding with two subsequent aspirations; convulsions reported as fainting; and expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain.”¹⁸⁵ After elaborating on the deficiencies found, the
 5 FDA inspector concluded: “Notwithstanding these objectionable conditions, [redacted name of an FDA official] assured Dr. Aubeny that he would not recommend that the studies not be included in the evaluation of the NDA application.”¹⁸⁶

FDA should not have allowed tainted data to support the Mifeprex NDA. A complete audit of all French Clinical Trial data is warranted to determine whether another set of clinical
 10 trials must be performed to replace the tainted French trial data.

F. THE AGENCY’S DE FACTO APPROVAL OF MISOPROSTOL’S NEW USE WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

15 When FDA approved Mifeprex, it also took action with respect to a second drug – misoprostol. Taken alone, mifepristone is ineffective as an abortifacient.¹⁸⁷ In order to achieve an abortion rate greater than 90 percent, the administration of mifepristone is followed approximately two days later by a prostaglandin to complete the abortion. In the U.S. Clinical

¹⁸⁴ Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1 [FDA FOIA Release: MIF 004135-45].

¹⁸⁵ Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1.

¹⁸⁶ Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 9.

¹⁸⁷ Although some studies using mifepristone alone have produced completion rates as high as 60 to 80 percent, it is widely recognized that, on its own, mifepristone is not a viable substitute for surgical abortion. *See, e.g.,* Mitchell D. Creinin, “Early Medical Abortion with Mifepristone or Methotrexate: Overview,” *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 3 (reporting that “[f]or gestations up to 49 days, complete abortion occurs in approximately 60% to 80%” of women using mifepristone alone); Helena von Hertzen, M.D., “Research on Regimens for Early Medical Abortion,” *Journal of the American Medical Women’s Association* 55 (Supplement 2000): 133-36.

Trial, the prostaglandin used was misoprostol, which was distributed by G.D Searle & Co.

("Searle") as the anti-ulcer drug CytotecTM.¹⁸⁸ Ultimately, FDA based its approval of Mifeprex on the combined action of a mifepristone and misoprostol regimen. On the day FDA approved mifepristone, it notified Searle that "[t]he drug mifepristone is now approved in a regimen with

5 misoprostol for termination of pregnancy of 49 days or less."¹⁸⁹

Searle, which opposed the use of its drug in conjunction with Mifeprex as an abortifacient,¹⁹⁰ did not file a Supplemental NDA for the use of misoprostol as part of an abortion regimen.¹⁹¹ Absent such an application, FDA lacked the basis for sanctioning a new indication for misoprostol. As Peter Barton Hutt, former FDA general counsel, observed, the agency's

10 treatment of misoprostol "set[] an extraordinary precedent" because FDA was "seemingly

¹⁸⁸ After a series of corporate transactions, Searle is now part of Pharmacia Corporation, which is headquartered in Peapack, New Jersey. In 1985, G.D. Searle & Co. became the pharmaceutical unit of Monsanto. In April 2000, Monsanto merged with Pharmacia & Upjohn to create the Pharmacia Corporation. Pharmacia & Upjohn had been created in 1995 when Pharmacia AB and the Upjohn Company merged. On July 15, 2002, Pfizer Inc. announced that it would purchase Pharmacia.

¹⁸⁹ Letter, Dr. Lilia Talarico, M.D., Director, FDA/CDER, Division of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III to Dr. Mary Jo Pritza, G.D. Searle & Co. (Sept. 28, 2000): at 1 [FDA FOIA Release: MIF 008847-48]. The Talarico Letter came in response to the August 8, 2000 application by Searle to obtain approval for changes that would have bolstered the Cytotec label's discussion of adverse effects (presumably in anticipation of FDA's approval of the mifepristone NDA). FDA chided Searle for attempting to make the proposed changes and summarily rejected them. *Id.* at 1. When it announced the Mifeprex approval, FDA referred to the "approved treatment regimen." See FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000). See also FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 4 (referring to the "mifepristone treatment regimen").

¹⁹⁰ In fact, on August 23, 2000, Searle wrote an open letter to all health care practitioners stating that "Cytotec is not approved for the induction of labor or abortion." The letter listed a number of potential "[s]erious adverse events reported following off-label use of Cytotec in pregnant women includ[ing] maternal or fetal death." Michael Cullen, M.D., Medical Director U.S., Searle, Open Letter to Health Care Providers (Aug. 23, 2000)[FDA FOIA Release: MIF 008022]. Officials of the American College of Obstetricians and Gynecologists, among others, decried Searle's lack of cooperation. See Ralph W. Hale, M.D., and Stanley Zinberg, M.D., "The Use of Misoprostol in Pregnancy," editorial, *New England Journal of Medicine* 344 (Jan. 4, 2001): 59-60. FDA's approval of the Mifeprex Regimen in the face of Searle's opposition appears to have usurped Searle's rights to control the distribution of its drug.

¹⁹¹ Because Searle's patent on misoprostol did not expire until July 2000, no other party would have been able to file a timely supplemental NDA for the use of a generic form of misoprostol as an abortifacient.

encouraging a drug's unapproved use."¹⁹² He added that the agency is in an "embarrassing and uncomfortable position."¹⁹³ FDA did more than encourage the unapproved use of misoprostol; it *mandated* the unapproved use.

5 1. **Misoprostol's Use as an Abortifacient is a New Indication for which the Requisite Supplemental New Drug Application Was Not Filed**

A drug that differs in any material way (including in composition, effect, or intended use) from an approved drug is a new drug that must independently be established to be safe and effective.¹⁹⁴ Furthermore, a drug already being used to treat one disease or part of the body may be a new drug when used to treat another disease or part of the body.¹⁹⁵ Misoprostol's new use as an abortifacient, therefore, marks it as a "new drug."¹⁹⁶

New drugs must be shown to be safe and effective. Specifically, FDA requires that "[a]ll indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) . . . unless the requirement is waived"¹⁹⁷

¹⁹² Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

¹⁹³ Zimmerman at B1.

¹⁹⁴ See *Thompson v. Western Medical Center*, Brief for the Petitioners (filed by the Solicitor General of the United States), No. 01-344 (Dec. 2001): at 4 ("See *United States v. Generix Drug Corp.*, 460 U.S. 453, 460-461 (1983) (determination whether a product is a new drug takes into account both active and inactive ingredients); 21 C.F.R. 310.3(h) (discussing factors that make a drug a 'new drug').

¹⁹⁵ A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

¹⁹⁶ The "newness" of misoprostol in this indication was heightened by the fact that, when Mifeprex was approved, misoprostol was explicitly contraindicated for pregnant women. The misoprostol label included the following black-box warning: "CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT . . ." In April 2002, the Cytotec label was changed to "remove[] the contraindication and precaution that Cytotec should not be used in women who are pregnant." FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). The label now restricts the contraindication to pregnant women who are using Cytotec as a non-steroidal anti-inflammatory drug ("NSAID"). The revised Cytotec label and, more specifically, the "Indications and Usage" section, however, continue to lack any reference to the use of misoprostol in the Mifeprex Regimen.

¹⁹⁷ 21 C.F.R. § 201.57(c)(2). To the best of the Petitioners' knowledge, FDA did not formally waive the requirement for misoprostol as part of an abortion regimen.

A Supplemental NDA provides the necessary evidence in support of a new indication.¹⁹⁸ Absent a waiver, a Supplemental NDA permits FDA to consider the evidence in support of the proposed change and approve related labeling changes in advance.¹⁹⁹ Even though a new use for misoprostol is an integral part of the Mifeprex Regimen, FDA sanctioned this new misoprostol indication without having received and considered a Supplemental NDA.

Among the changes for which FDA approval is necessary are changes to statements in a drug's labeling indicating whether "[t]he drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy."²⁰⁰ A well-known treatment regimen illustrates how FDA has typically dealt with the labeling of two drugs that have been approved for combined use. The regimen pairs methotrexate and Leucovorin Rescue. Methotrexate, a chemotherapeutic agent, kills cancer cells by depriving them of folic acid which is necessary for DNA synthesis, but, in the process, methotrexate deprives normal bone marrow cells of the folic acid they need. Leucovorin Rescue serves as an antidote to the toxic effects of methotrexate. The labeling for Leucovorin Rescue refers to its use "after high-dose methotrexate therapy in osteosarcoma," which is an approved

¹⁹⁸ A recent article noted: "To obtain FDA approval for an additional use of a previously approved drug, the sponsor must submit a supplemental application (sNDA, sBLA, or sPMA) demonstrating the safety and efficacy of the drug when used in the new way or for the new indication. The supplemental application typically requires clinical data similar to those in the original application, but does not require the same extensive chemistry, manufacturing and controls, and preclinical pharmacology and toxicology data as in the original application." Shane M. Ward, "Washington Legal Foundation and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet," *Food and Drug Law Journal* 56 (2001): 41-56, at 44 (citations omitted).

¹⁹⁹ See 21 C.F.R. § 314.70(b). See also Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1775 ("FDA takes the position, which no manufacturer has sought to challenge in court, that any potentially significant modification of an approved new drug [application] likewise requires advance agency approval. As a consequence, not only attempts to expand the indications for a drug but other changes in labeling, in inactive ingredients, in the method or location of manufacture, or in packaging must first be the subject of an approved Supplemental New Drug Application.").

²⁰⁰ See 21 C.F.R. § 201.57(c)(1)(iv).

indication for methotrexate.²⁰¹ Similarly, methotrexate's labeling refers to an approved use of Leucovorin Rescue.²⁰²

By contrast, in the Mifeprex labeling, an *unapproved* indication for misoprostol is discussed. In approving such labeling, FDA has taken the aberrant position that the maker of one drug (Mifeprex) can secure approval of a new indication for another company's drug (misoprostol) merely by describing that new use as part of a combined therapy. FDA circumvented its own regulations by failing to require that both drugs in the Mifeprex Regimen be approved for the indication in question – pregnancy termination.²⁰³

²⁰¹ See Leucovorin Calcium for Injection Package Insert ("Indications and Usage") ("Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists."). The package insert is available at: <http://www.xanodyne.com/leucovorin_calcium_pl_2002.pdf>.

²⁰² The methotrexate package insert states that "[m]ethotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor." The package insert is available at: <http://www.rxlist.com/cgi/generic/mtx_ids.htm>.

²⁰³ A recent approval of a biologic product also illustrates the principle that FDA-approved labeling lists only approved indications. On February 19, 2002, FDA approved Zevalin for use in combination with Rituxan (rituximab) to treat low-grade B-cell non-Hodgkins Lymphoma (NHL). Rituxan had been approved previously and was already indicated "for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma." See Rituxan Package Insert ("Indications and Usage"). Rituxan and Zevalin are monoclonal antibodies that can significantly shrink tumors by targeting white blood cells (B-cells) including malignant B cells. The "Indications and Usage" section of Zevalin's label describes the drug as being "part of the ZEVALIN therapeutic regimen (see Dosage and Administration)." The "Dosage" section directs that Rituxan be administered and then followed by Zevalin on Day One and then again seven to nine days later. After the Zevalin NDA was approved, detailed information about the administration of the "Zevalin Therapeutic Regimen" was added to the Rituxan label. On February 19, 2002, FDA's Center for Biologics Evaluation and Research approved a supplement to the Rituximab biologics license application "to revise the dosage and administration section of the package insert to include information regarding the use of Rituximab as a component of the Zevalin therapeutic regimen" Letter, Dr. Karen D. Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, to Alice Wei, IDEC Pharmaceuticals (Feb. 19, 2002) (see <<http://www.fda.gov/cber/approvltr/rituide021902L.htm>>).

2. FDA Sanctioned the Promotion of Misoprostol for an Unapproved Use as Part of the Mifeprex Regimen

The use of misoprostol as an abortifacient is an unapproved or “off-label” use.²⁰⁴ FDA objects to the *promotion* of off-label uses of drugs by manufacturers.²⁰⁵ “Off-label” uses of drugs are common as physicians explore new ways of using approved drugs, but normally FDA strives to ensure that physicians and patients are not misled into believing that FDA has approved such uses. In an effort to curb the promotion of off-label uses by pharmaceutical manufacturers, FDA issued regulatory guidance in 1996 pertaining to the dissemination of off-label use information.²⁰⁶

In this case, however, FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol. FDA oversaw the creation of the promotional materials for Mifeprex,²⁰⁷ which discussed the off-label use of misoprostol.²⁰⁸ FDA itself disseminated information about

²⁰⁴ See generally James M. Beck and Elizabeth D. Azari, “FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions,” *Food & Drug Law Journal* 53 (1998): 71-104, at 71 n.2, which explains “off-label” use as follows:

“Off-label” has more accurately been termed “extra label” use. It means only that a product is used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely. See, e.g., *Washington Legal Found. v. Kessler*, 880 F.Supp. 26, 28 n.1 (D.D.C. 1995). . . . Off-label can mean many things. “[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use.” William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (footnotes omitted).

²⁰⁵ See, e.g., *Subpart H Final Rule*, 57 Fed. Reg. at 58,953 (“Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug’s safety and effectiveness have been established and that FDA has approved.”).

²⁰⁶ See FDA, “Advertising and Promotion; Guidances,” Notice, 61 Fed. Reg. 52,800 (Oct. 8, 1996) (publishing two guidance documents: “Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data” and “Guidance for Industry Funded Dissemination of Reference Texts”).

²⁰⁷ FDA reminded the Population Council in the Mifeprex Approval Letter that, pursuant to 21 C.F.R. § 314.550, the drug sponsor is obligated to submit Mifeprex promotional material for review by the agency prior to dissemination to physicians and the public. See Mifeprex Approval Letter at 3.

²⁰⁸ A Danco Laboratories webpage, for example, contains the following question and answer:

Q: How Does Mifeprex Work?

A: Mifeprex blocks progesterone, a hormone necessary for a pregnancy to continue. You take Mifeprex followed by a prostaglandin, misoprostol, which causes uterine contractions that help to end pregnancy.

In more detail, Mifeprex blocks progesterone, a naturally produced hormone that prepares the lining of the uterus for a fertilized egg and helps maintain pregnancy. Without progesterone, the lining of the uterus

the off-label use of misoprostol in documents such as the press release announcing the approval of Mifeprex for use in conjunction with misoprostol.²⁰⁹ Recently it did so again when the agency emphasized the importance of adhering to the approved regimen, including the off-label use of misoprostol.²¹⁰

3. Mifeprex Is Misbranded: Its Labeling Promotes an Unapproved Use of Another Drug

The labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved.²¹¹ FDA's ability to regulate the marketing and distribution of drugs rests largely on its legal capacity to strictly control the content of a drug's labeling. A fundamental tenet of drug regulation is that FDA requires approval for every indication listed in the labeling of a drug.²¹² FDA would undercut its own authority if it did not also apply this rule to uses for a drug referenced on another drug's labeling.

The Mifeprex labeling creates false expectations about misoprostol. Physicians and patients are justified in believing that any use or indication for a drug, included in the "Indication

softens, breaks down and bleeding begins. Mifeprex is followed by a prostaglandin that causes the uterus to contract, which helps to complete the process. . . . The prostaglandin used following Mifeprex is misoprostol, a drug already available in the United States.

"Using Mifeprex: Frequently Asked User Questions," Danco Laboratories website at <http://www.earlyoptionpill.com/may_faqs.php3>. The electronic version of the Mifeprex Label contains a hyperlink to the Danco Laboratories website, <www.earlyoptionpill.com>, which contains the above-referenced webpage. (When printed, the hyperlink appears to be ordinary text.)

²⁰⁹ See, FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000) ("Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin.").

²¹⁰ See FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 6. In this same document, however, FDA cautions health care providers against "using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses . . ." *Id.* at Question 9.

²¹¹ Misoprostol receives more than a passing mention on the Mifeprex Label; the word "misoprostol" appears 34 times (compared to 57 appearances of "mifepristone" and 34 appearances of "Mifeprex").

and Usage” section of an FDA-approved label, has been subjected to the rigorous approval process set forth in Section 505 of the FD&C Act. Section 201.6(a) of the Agency’s rules states that misbranding may arise from “a false or misleading representation with respect to another drug.”²¹³ “When a physician, manufacturer, or *other third party* steps in to promote an unapproved use of a drug by advertising or distribution to other physicians, the drug may become unlawful under Section 301(k) the FD&C Act, 21 U.S.C. § 331(k)(1994), which prohibits misbranding, and Section 502(f)(1), 21 U.S.C. § 352(f)(1)(1994), which requires a drug’s labeling to bear ‘adequate directions for use.’”²¹⁴ Mifeprex is, therefore, misbranded.

Mifeprex is also misbranded because it is unsafe when used as directed in the approved labeling. Section 502(j) of the FD&C Act states that “[a] drug or device shall be deemed to be misbranded . . . [i]f it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.”²¹⁵ As discussed in the next section, FDA’s approved regimen is unsafe because it lacks important safeguards.

²¹² See Elizabeth A. Weeks, “Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997,” *Food and Drug Law Journal* 54 (1999): 645-65, at 647 n.13 (citing Merrill, *infra* Appendix A), at 1853).

²¹³ See 21 C.F.R. § 201.6(a).

²¹⁴ Merrill, *infra* Appendix A, at n.318 (emphasis added). See also 21 C.F.R. § 314.530(a)(5) (authorizing the Secretary to withdraw approval of a Subpart H drug if “[t]he promotional materials are false or misleading”).

²¹⁵ 21 U.S.C. § 352(j). See also Jeffrey N. Gibbs and Judith E. Beach, “Chapter 7: Adulteration and Misbranding of Drugs” in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 229 (“When the drug is dangerous to the health of the user even when used as recommended on the label, it is misbranded.”).

G. WOMEN'S LIVES ARE BEING ENDANGERED BY THE LACK OF SAFEGUARDS IN FDA'S APPROVED REGIMEN

5 On February 18, 2000, FDA informed the Population Council that “adequate information ha[d] *not* been presented to demonstrate that [mifepristone], when marketed in accordance with the terms of distribution proposed [by the Population Council], is safe and effective for use as recommended.”²¹⁶ Over the next several months, the Population Council and Danco refused to supplement its distribution plan with a meaningful patient safety component. This prompted
10 FDA, on June 1, 2000, to privately convey to the sponsor a set of proposed restrictions intended to rectify the sponsor’s omission. The agency’s proposed restrictions were soon leaked to the public. Amidst a vigorous political and editorial backlash, the sponsor not only rejected FDA’s proposal but, in what was described by FDA as a “very significant change,” repudiated
15 restrictions the sponsor itself had proposed in 1996.²¹⁷ FDA succumbed and soon approved a regimen that did not embody restrictions sufficient to address the agency’s legitimate safety concerns.

Early in the approval process, FDA expressed its intention to place restrictions on the use of mifepristone.²¹⁸ FDA’s position was informed, in part, by the international experience with

²¹⁶ 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5 (emphasis added).

²¹⁷ See FDA Email (June 23, 2000): at 1 (explaining that the Population Council’s attorney “affirmed that the 1996 proposals for distribution system as presented by the Pop Council then and agreed to by the [FDA Advisory Committee] and FDA are NOT what the Pop Council wants today. I explained that this change is very significant and that they need to provide their justification/rationale.”)[FDA FOIA Release: MIF 002523].

²¹⁸ In order to allay concerns of the drug’s European owner, FDA pledged, in the course of securing the U.S. patent rights for the Population Council, to “take appropriate measures . . . to assist through the NDA-approval process in the creation of a regime for the distribution and use that will protect against misuse of the drug.” Letter, David A. Kessler, Commissioner of Food and Drugs, to the President & CEO of Roussel Uclaf [name redacted] and to Margaret Catley-Carlson, President of Population Council (May 16, 1994): at 1 [FDA FOIA Release: MIF 004992-93].

mifepristone.²¹⁹ The NDA submitted by the Population Council on March 14, 1996 included a plan that would have limited distribution of mifepristone to “licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted]), who will attend educational seminars on the safe use of this regimen.”²²⁰

5 The FDA Advisory Committee, when it met in July 1996, was not satisfied with the restrictions proposed by the Population Council and expressed “serious reservations on how [the proposed drug distribution system] is currently described in terms of assuring safe and adequate credentialing of providers.”²²¹ The Committee recommended additional restrictions designed to ensure “that this drug not be expanded to hands of physicians who are not already skilled in
10 managing pregnancies, terminations, and complications of both.”²²² Accordingly, FDA’s 1996 Approvable Letter required the submission of “a comprehensive description of the proposed distribution system.”²²³

In subsequent submissions, however, the Population Council insisted that the drug was safe and proffered restrictions designed primarily to control the manufacturing and retailing of
15 the drug product. On August 18, 1999, the Population Council proposed to:²²⁴ (i) limit the number and type of distributors; (ii) limit distribution to distributor-registered physicians who

²¹⁹ In Europe, for example, mifepristone is used under more highly controlled conditions than were ultimately required in the United States. See Amendment to NDA 20-687, International Product Labeling with English Translations (submitted March 21, 2000) (presenting English translation of mifepristone product label, approved July 6, 1999, used in Austria, Belgium, Denmark, France, Germany, Greece, the Netherlands and Spain)[FDA FOIA Release: MIF 000493-506].

²²⁰ Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62].

²²¹ FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45].

²²² FDA Memorandum, “Highlights of the July 19, 1996 Reproductive Health Products Advisory Committee (AC) Meeting on Mifepristone: Outstanding Issues for FDA to Address” (undated): at 3-4 [FDA FOIA Release: MIF 000534-38].

²²³ 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 1.

had provided certain assurances;²²⁵ and, (iii) make available “training materials and information” and medical consultation to health care providers and product information to patients.²²⁶ On January 21, 2000, Danco opined that “[r]egardless of the distribution system for mifepristone, the medical safety of this drug is well documented.”²²⁷ and proposed a distribution system that was

5 designed only to ensure that Danco would “exert[] positive control over distribution of Mifeprex[®] through all phases of manufacturing, storage, shipment and administration from manufacturer to patient.”²²⁸

In reaction to the sponsor’s recalcitrance, FDA took the position “that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this

10 product.”²²⁹ The agency nevertheless continued to encourage the sponsor to take an active role in devising appropriate restrictions on the use of mifepristone. Instead, in March 2000, the Population Council again protested that such restrictions were unwarranted.²³⁰ It submitted a

²²⁴ See Medical Officer’s Review, *infra* Appendix A, at 21-23 (setting forth the Population Council’s complete response submitted to FDA on August 18, 1999).

²²⁵ The physician would be required to provide a *self*-attestation covering the physician’s ability to accurately date pregnancies and determine the patient’s blood Rh factor and the physician’s access to emergency medical facilities. Registering physicians would also agree to obtain from each patient an acknowledgement that she has received full information and is willing to comply with the treatment regimen, to maintain certain records (including ultrasound and blood test records) for each patient, to report adverse events and information about ongoing pregnancies, and to “[u]se every effort to ensure patients return for their follow up visit 14-20 days after taking the product.” See Medical Officer’s Review, *infra* Appendix A, at 22-23.

²²⁶ See Medical Officer’s Review, *infra* Appendix A, at 23.

²²⁷ Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26]. Danco attempted to attribute any deleterious effects of mifepristone abortions to misoprostol: “More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin.” *Id.* at 2.

²²⁸ See Amendment 039 to the NDA, Mifeprex Distribution Plan Executive Summary (Jan. 21, 2000): at 3 [FDA FOIA Release: MIF 000530-31].

²²⁹ See 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5. See *supra* Section III.C.2 and III.D. for a discussion of Subpart H, Section 314.520, which is reserved for drugs that are so inherently dangerous that their distribution and use must be restricted.

²³⁰ In the course of objecting to the approval of the drug under subpart H, which is “likely to falsely ‘mark’ mifepristone as a highly toxic and risky drug,” the Population Council insisted that “the FDA knows, [Mifeprex] is

distribution plan that it characterized as “detailed and comprehensive” and “surely equal to its purpose.”²³¹ Once again, the plan consisted of restrictions intended only to control the manufacturing and retailing of the drug product.²³² Again FDA objected that “[t]he proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient.”²³³ The agency requested “that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product.”²³⁴

On June 1, 2000, FDA proposed the following set of “Qualifications for Physician Recipients:” (1) the physician must demonstrate that she is licensed to practice medicine; (2) the physician must be “trained and authorized by law” to perform surgical abortions; (3) the physician must have “been trained to and ha[ve] the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination;” (4) the physician must have “satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications;” and

exceptionally safe and effective.” Responses by Population Council to “FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)” (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24] (“March 2000 Response”).

²³¹ March 2000 Response, *infra* Appendix A, at 2.

²³² Specifically, the plan provided for “secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements.” March 2000 Response, *infra* Appendix A, at 2.

²³³ Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1 [FDA FOIA Release: MIF 007811-13].

²³⁴ Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1. FDA wanted the sponsor to provide a set of auditable provider qualifications, a plan for auditing providers to ensure that they were meeting these criteria, and an arrangement for discontinuing distribution to unqualified providers. *See id.* at 2.

(5) the physician must have “continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour’s] drive from the treatment facility.”²³⁵ FDA’s proposals were intended to address concerns about the safety of the women undergoing mifepristone-

5 misoprostol abortions that the Population Council and Danco had refused to take into account in crafting restrictions for the drug.²³⁶

The Population Council and Danco objected strenuously to the proposed restrictions and aired their complaints in public.²³⁷ FDA reprimanded the Population Council for leaking the restrictions to the public and misrepresenting the nature of the restrictions.²³⁸ The Executive Vice

10 President of the American College of Obstetricians and Gynecologists submitted an analysis of the leaked restrictions to FDA.²³⁹ The editorial and political reaction,²⁴⁰ together with the

²³⁵ See FDA, “FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00” (June 1, 2000)[FDA FOIA Release: MIF 000522]. See also American College of Obstetricians and Gynecologists, “Analysis of the Possible FDA Mifepristone Restrictions” (July 27, 2000): at 1 (setting forth FDA’s second proposed restriction, which is redacted in the publicly available copy of FDA’s proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

²³⁶ It should be noted, that even these restrictions would not have been sufficient to make mifepristone-misoprostol abortions safe. Among the key safeguards missing from FDA’s proposal were requirements that every prospective patient undergo an ultrasound and that prescribing physicians be required to have admitting privileges at facilities able to provide emergency care.

²³⁷ Paul Blumenthal, M.D., Jane Johnson, and Felicia Stewart, M.D., “The Approval of Mifepristone (RU486) in the United States: What’s Wrong with this Picture?” *Medscape Women’s Health* 5 (2000) (reproduced in an internal FDA email)[FDA FOIA Release: MIF 00002597-99] (“At a meeting of early abortion providers and abortion advocates, the Population Council and Danco revealed that the U.S. Food and Drug Administration (FDA) had made a series of proposals regarding the labeling and distribution of mifepristone that would severely limit women’s access to the drug if and when it is approved.”).

²³⁸ See Teleconference Meeting Minutes (between FDA staff and representatives of the Population Council and Danco) (June 7, 2000): at 1 (“Meeting Objective: . . . to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.”)[FDA FOIA Release: MIF 002136-37]; FDA internal email (June 23, 2000): at 1 (re: telephone conversation with Population Council attorney, Nancy Buc, on 6/23/00) (“I also said that we were looking to Pop Council to be a responsible entity in manufacturing, distributing, and shepherding this drug and that most responsible entities make proposals rather than expect FDA to write labels and distribution systems and obtain comments through the media.”)[FDA FOIA Release: MIF 002523].

²³⁹ See Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) to Jane Henney, M.D. (July 24, 2000) and enclosure: ACOG, “Analysis of the Possible FDA Mifepristone Restrictions” (July 27, 2000)[FDA FOIA Release: MIF 001366-69]. ACOG and the American Medical Association (“AMA”) also attempted to secure a meeting with

impending approval deadline of September 30, 2000,²⁴¹ however, had the desired effect of undermining FDA's resolve.

At a meeting on July 19, 2000, FDA yielded to the Population Council and Danco on a number of important issues.²⁴² FDA abandoned its proposal for auditable physician

5 qualifications and agreed instead to permit physicians to attest to their own qualifications.²⁴³

Instead of requiring formal training, FDA merely "request[ed] that the physician also attest to having read and understood the training materials and labeling."²⁴⁴ FDA also agreed not to

Dr. Jane Henney, FDA Commissioner, and her staff, in order to further discuss their opinion of the restrictions. *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) and E. Ratcliffe Anderson, Jr., M.D. (Executive Vice President, AMA) to Jane Henney, M.D. (July 24, 2000): at 1 ("The undersigned organizations . . . are very concerned about restrictions . . . [FDA] has proposed for . . . mifepristone. . . . We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely from political influence.") [FDA FOIA Release: MIF 001363]. They were permitted only to meet with officials in FDA's Office of Women's Health, an office within the agency that was not involved in reviewing the NDA. *See* Letter, Jane Henney to Hale and Anderson (Aug. 11, 2000): at 1-2 [FDA FOIA Release: MIF 001361]. The questionable scientific basis for this challenge to FDA's proposed restrictions was recently brought to the attention of ACOG by one of the Petitioners. Letter, Donna Harrison, M.D. (Chairperson, AAPLOG Committee on Mifeprex Use) to Ralph Hale, M.D. (Executive Vice President, ACOG) (May 23, 2002) (available at <<http://www.aaplog.org/acogmifeprexletter.htm>>).

²⁴⁰ *See, e.g.*, Letter, U.S. Senator Barbara Boxer to Dr. Jane Henney (June 9, 2000): at 1 ("According to news reports, the FDA is considering placing draconian restrictions on the accessibility of RU-486 as a condition of its approval In 1996, the FDA found RU-486 to be safe and effective. Therefore, it is a mystery to me why the FDA would even consider restricting access to it.") [FDA FOIA Release: MIF 006376]; Letter, Mark Green, Public Advocate for the City of New York, to Dr. Jane Henney (Sep. 22, 2000): at 1 ("Earlier this week Planned Parenthood of New York City, NARAL-New York, the Access Project and Physicians for Reproductive Health and Choice joined me in convening a public hearing in New York City on pending action by [FDA] on mifepristone [I am] also concerned about the restrictions on access to RU-486 that FDA is said to be considering.") [FDA FOIA Release: MIF 001288-1302]; Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times* (June 8, 2000): at A21 ("The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by [FDA] that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it."); Letter, U.S. Representative Lynn Woolsey to Dr. Jane Henney (June 22, 2000): at 1 ("However, I am deeply concerned about recent press reports about proposed restrictions.") [FDA FOIA Release: MIF 006372].

²⁴¹ As noted above, because FDA had accorded priority review to mifepristone, the approval process was slated for completion by September 30, 2000.

²⁴² *See* Meeting Minutes, re: Approvability Issues Related to Labeling and Distribution Plan for Mifepristone (July 19, 2000): at 2-4 [FDA FOIA Release: MIF 004661-65].

²⁴³ *See id.* at 2.

²⁴⁴ *Id.* at 2.

require pre-procedure ultrasounds.²⁴⁵ Furthermore, FDA stated “that it is not necessary to require the patient to take the drugs in the presence of health care provider.”²⁴⁶

Among the unresolved issues at the conclusion of the July 19, 2000 meeting was the question of whether prescribing physicians should be limited to those who were able to perform surgical abortions, a provider qualification FDA believed was necessary:

FDA requests that the ability to perform vacuum aspirations and/or D&Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women’s health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.²⁴⁷

The Population Council later rejected FDA’s request,²⁴⁸ and the agency acquiesced.²⁴⁹

Despite its persistent concerns, FDA approved a regimen that posed the very risks to women’s health that the agency had previously identified. When it approved Mifeprex, FDA stated that “[u]nder 21 CFR 314.520, distribution of the drug is restricted as follows:”

MifeprexTM must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of MifeprexTM.

²⁴⁵ See *id.* at 3.

²⁴⁶ *Id.* at 3.

²⁴⁷ *Id.* at 3.

²⁴⁸ See Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 6 (arguing that bolstering the provider qualifications in this way would be “not only unnecessary, but also in fact potentially counterproductive for patients”)[FDA FOIA Release: MIF 0001373-81].

²⁴⁹ See Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 [FDA FOIA Release: MIF 004587-88].

- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement, and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's records.²⁵⁰

In addition, the restrictions include a requirement that distribution be carried out in accordance

with the plan submitted to FDA by the Population Council in a March 30, 2000 submission.²⁵¹

Even as it assented to a regimen that lacked critical safeguards, FDA took a number of steps that indicated its lingering concerns about the safety of the drug. First, FDA ultimately decided to rely on an infrequently used provision in Subpart H in hopes of ensuring that mifepristone would be used safely and, if necessary, could be withdrawn from market rapidly.²⁵² Second, the staff insisted that the mifepristone label "include a black boxed warning describing the major requirements and conditions for use."²⁵³ "FDA generally reserves boxed warnings for serious or

²⁵⁰ Mifeprex Approval Letter at 2.

²⁵¹ See Mifeprex Approval Letter at 2.

²⁵² See 21 C.F.R. 530 ("Withdrawal Procedures"). See also FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85]. As late as July 19, 2000, the question of whether to use Subpart H was deemed to be an "Outstanding Issue." See Meeting Minutes, re: Approvability Issues (July 19, 2000): at 4 [FDA FOIA Release: MIF 004661-65].

²⁵³ FDA, Memorandum, re NDA 20-687 (Feb. 17, 2000): at 2. The Population Council, which opposed the inclusion of such a warning, ultimately persuaded FDA to agreed to a pared-down Black Box Warning, which would merely direct the prescribing physician (i) to plan in advance for emergency care, and (ii) to make available to the patient and provide her with the opportunity to discuss the patient information and patient agreement. See Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 1-2 [FDA FOIA Release MIF 0001373-81].

life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner.”²⁵⁴

FDA’s willingness to tailor the restrictions on Mifeprex to suit the demands of the Population Council and Danco will continue to manifest itself in serious adverse events among the women who use the Mifeprex Regimen. Some of the most critical flaws in the approved regimen are discussed below along with serious adverse events that have already been reported.

1. The Approved Regimen Is Unsafe Because It Does Not Require Ultrasound

a. Ultrasound Is Necessary to Accurately Date Pregnancies

The gestational age of a woman’s pregnancy is a critical factor in determining whether she is an appropriate candidate for a mifepristone abortion. In order to minimize the risks of hemorrhage, incomplete abortion and continuing pregnancy, the gestational age of the pregnancy must be less than or equal to 49 days.²⁵⁵ The authors of the Spitz Article, for example, found that “[f]ailures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of the pregnancy.”²⁵⁶ Through the combination of mifepristone and

²⁵⁴ Judith E. Beach et al., “Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs,” *Food and Drug Law Journal* 53 (1998): 403-412, at 403 (available at: http://www.fdpi.org/pubs/Journal%20Online/53_3/art2.pdf). See also 21 C.F.R. § 201.57(e) (“Warnings”).

²⁵⁵ As noted above, the gestational age of a pregnancy is based on the first day of a woman’s last menstrual period, which is designated as Day 1 of the pregnancy.

²⁵⁶ Spitz Article, *infra* Appendix A, at 1241. “The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the [less than or equal to] 49-days group to 9 percent in the 57-to-63 days group (P<0.001).” Children born from ongoing pregnancies, after a failed application of the Mifeprex Regimen, may suffer birth defects, fertility problems, or other health problems later in life. Researchers have found evidence linking misoprostol and birth defects such as missing or deformed limbs and misshapen skulls. Much of this research was conducted in Brazil, where numerous women have attempted to induce abortions using misoprostol alone. See, e.g., Sylvia Pagán Westphal, “Birth Defects Caused by Ulcer Drug Abortions,” *NewScientist.com* (29 Aug. 2001) (“Several studies in Brazil, where up to 75 percent of clandestine abortions involve misoprostol, suggest the drug causes birth defects such as fused joints, growth retardation and a condition known as Möbius syndrome, which is characterised by paralysis of the face.”); Iêda M. Orioli and Eduardo E. Castilla, “Epidemiological

misoprostol, “pregnancy was terminated in 762 of the 827 women pregnant for [less than or equal to] 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent)”²⁵⁷ The study also found that “[a]bdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age.”²⁵⁸ Due to the significant increase in failures and complications with increasing gestational age, FDA approved Mifeprex only for pregnancies of less than or equal to 49 days’ gestation.²⁵⁹

The only way to date a pregnancy with the degree of accuracy necessary to exclude women whose pregnancies are beyond 49 days’ gestation is by use of transvaginal ultrasound.

FDA severely undermined the limitation on gestational age, however, when it failed to require

Assessment of Misoprostol Teratogenicity,” *British Journal of Obstetrics and Gynaecology* 107 (April 2000): 519-23, at 522 (“ . . . there is an association of prenatal use of misoprostol as an abortifacient and congenital defects of vascular disruption type.”); F.R. Vargas *et al.*, “Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case-Control Study,” *American Journal of Medical Genetics* 95 (2000): 302-306, at 306 (“add[ing] epidemiological basis to the growing body of evidence that prenatal exposure to misoprostol is related to the occurrence of vascular disruption defects in some exposed fetuses.”). FDA determined that data submitted by the Population Council from a survey of fetal abnormalities in 82 pregnancies that were exposed to mifepristone alone or in combination with misoprostol was inconclusive. See FDA Mifeprex Approval Memorandum, *infra* Appendix A, at 4. FDA acknowledged, however, the possible link between misoprostol and birth defects. See Medical Officer’s Review, *infra* Appendix A, at 18 (“ . . . medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).”). The need for a study of the possible joint effects of mifepristone and misoprostol on babies born after a failed application of the Mifeprex Regimen was highlighted by the abnormalities discovered in a fetus exposed to misoprostol and mifepristone. See Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Number 3877547-X (March. 1, 2002) (French report of numerous deformities in fetus that was exposed to mifepristone and misoprostol but survived until a subsequent surgical abortion was performed; “The anatomopathology examination showed a meningo-encephalocele. The left hand was constituted of only two fingers (oligodactylia), left and right foot were constituted of only one finger (monodactylia). There was a facial dysmorphism.”).

²⁵⁷ Spitz Article, *infra* Appendix A, at 1241.

²⁵⁸ Spitz Article, *infra* Appendix A, at 1241. In order to treat vaginal bleeding, “[t]wo percent of the women in the [less than or equal to] 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids (P=0.008).” *Id.*

²⁵⁹ FDA’s Medical Officer’s Review noted: “The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age.” Medical Officer’s Review, *infra* Appendix A, at 18. The review stated further: “This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period.” *Id.*

the ultrasound dating of pregnancies. FDA's approved regimen relies instead on a patient's recollection of her menstrual history and a physical examination. Dating based on menstrual history is inherently inaccurate because women may not have a perfect 28-day menstrual cycle²⁶⁰ and because 25 percent of women experience bleeding during the early stages of pregnancy.²⁶¹

5 Gestational dating through physical examination, even when carried out by experienced clinicians, can also be inaccurate.²⁶² Factors such as patient body size, uterine fibroids, previous parity, and uterine position may impair a clinician's ability to assess uterine size.²⁶³ Transvaginal ultrasound, by contrast, is accurate within plus or minus 3 days at gestational ages of 5 to 7 weeks.²⁶⁴ "Transvaginal ultrasonographic examination is necessary to ensure accurate gestational

²⁶⁰ See, e.g., Leon Speroff, M.D., Robert H. Glass, M.D., and Nathan G. Kase, M.D., *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 219 ("The perfect 28 day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's cycles. Overall, approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days. Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles.").

²⁶¹ See Peter W. Callen, M.D., *Ultrasonography in Obstetrics and Gynecology* 2nd ed. (Phila, Pa: W.B.Saunders Company; Harcourt, Brace, Jovanovich, 1988) at 32 ("Threatened abortion is a common complication that occurs in approximately 25% of clinically apparent pregnancies."); Speroff, *et al*, *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 536 (noting that "pregnancy and pregnancy-related problems such as ectopic pregnancy or spontaneous abortion" can cause uterine bleeding).

²⁶² Steven R. Goldstein, M.D., Francis R. M. Jacot, M.D., Claude Poulin, M.D., and D. Scott Poehlmann, M.D., "Documenting Pregnancy and Gestational Age," Chapter 4, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 41 ("Although clinical sizing of the uterus during the first trimester can provide a rough estimate of gestational age, it is imprecise; misestimation of gestational age by uterine sizing alone can occur even in the hands of experienced clinicians.").

²⁶³ See *A Clinician's Guide*, *infra* Appendix A, at 41 ("a number of conditions such as leiomyomas, multiple gestation, and obesity may severely limit the accuracy of gestational age assessment by physical examination, warranting preprocedure assessment by ultrasonography in known or suspected cases") (footnotes omitted).

²⁶⁴ See Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," *American Journal of Obstetrics and Gynecology* 168 (March 1993): 903-908; Ivar K. Rossavik, M.D., George O. Torjusen, M.D., and William E. Gibbons, M.D., "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in *in Vitro* Fertilization Pregnancies," *Fertility and Sterility* 49 (1988): 1012-17. See also Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and Gynecology* 180 (1999): 35-41. In this study comparisons of gestational age estimates based on the last reported menstrual period to those generated through ultrasound in patients presenting for medical abortion, revealed the former method to be significantly inaccurate in approximately half the cases. The authors observed: "It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified

dating for provision of medical abortion according to current standards in clinical guidelines established by the National Abortion Federation.”²⁶⁵

b. Ultrasound Is Necessary to Identify Ectopic Pregnancies

Approximately two percent of all pregnancies in the United States are “ectopic pregnancies,” in which the pregnancy is located outside the uterus – often in the fallopian tube.²⁶⁶ Mifeprex does not terminate ectopic pregnancies.²⁶⁷ Therefore, if a woman who has an ectopic pregnancy undergoes a mifepristone-misoprostol abortion, she is at risk for tubal rupture and subsequent hemorrhage due to delay in diagnosis and delay in treatment. The symptoms of an ectopic pregnancy – vaginal bleeding, pelvic pain, and cramping – are confusingly similar to certain side effects of the Mifeprex Regimen.²⁶⁸ A woman with an ectopic pregnancy is at risk of suffering massive intra-abdominal hemorrhage, damage to her reproductive organs, permanent

by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included.” *Id.*

²⁶⁵ Mitchell D. Creinin, M.D. and Heather Jerald, “Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria,” *American Journal of Obstetrics and Gynecology* 180 (1999): at 35-41 (text preceding n. 8) (citation omitted).

²⁶⁶ Centers for Disease Control, “Ectopic pregnancy – United States, 1990-1992,” *Morbidity and Mortality Weekly Report (MMWR)* 44 (No. 3) (Jan. 27, 1995): at 46. The number of ectopic pregnancies may be even higher now because sexually transmitted diseases and other causes of ectopic pregnancy are more widespread than they were in 1992 – the latest year for which the Centers for Disease Control have reported the number of ectopic pregnancies. *Id.* at 46-7.

²⁶⁷ See, e.g., Beth Kruse *et al.*, “Management of Side Effects and Complications in Medical Abortion,” *American Journal of Obstetrics and Gynecology* 183 (2000): S65-S75, at S72 (“Mifepristone has not proved effective in treating extrauterine pregnancy . . .”).

²⁶⁸ See American College of Obstetricians and Gynecologists, “Medical Management of Abortion,” *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists* 26 (April 2001): at 6 (noting that in medical abortions, “women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy”) (“ACOG Practice Bulletin”). Vaginal bleeding, for example, is a normal consequence of the Mifeprex Regimen and may continue for weeks after a woman ingests Mifeprex and misoprostol. See, e.g., Spitz, *infra* Appendix A, at 1243 (“Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated

sterility, and even death if not promptly treated by emergency surgery. The authors of a French mifepristone study in which a participant with an ectopic pregnancy underwent emergency surgery to stop heavy bleeding, concluded that:

5 The case of undiagnosed ectopic pregnancy, which ruptured suddenly 2 days after misoprostol intake, indicates that (1) mifepristone plus misoprostol is not an effective treatment of ectopic pregnancies and should not be used for this purpose, and (2) all medical means of detecting an ectopic pregnancy should be used before prescribing mifepristone plus misoprostol.²⁶⁹

10 Although the Mifeprex Label states that the Mifeprex Regimen is contraindicated for women with a “[c]onfirmed or suspected ectopic pregnancy,”²⁷⁰ FDA did not require that ultrasound be used to exclude women with ectopic pregnancies. Instead, the approved regimen relies solely on a self-certification by the prescribing physician that she has the “[a]bility to diagnose ectopic pregnancies.”²⁷¹ A physical examination alone cannot accurately identify
15 ectopic pregnancies. Ultrasound, “[i]n addition to providing the best information for gestational age determination . . . can also provide useful diagnostic information regarding a wide variety of pathologies of early pregnancy,” including ectopic pregnancies.²⁷²

medically. The median duration of bleeding or spotting was 13 days in the [less than or equal to] 49-days group and 15 days in the other two groups ($P < 0.001$).”).

²⁶⁹ Elizabeth Aubény, *et al.*, “Termination of Early Pregnancy (Up to 63 Days of Amenorrhea) with Mifepristone and Increasing Doses of Misoprostol,” *International Journal of Fertility & Menopausal Studies* 40 (1995): 85-91, at 91.

²⁷⁰ See Mifeprex Label (“Contraindications”).

²⁷¹ See Mifeprex Prescriber’s Agreement.

²⁷² *A Clinician’s Guide*, *infra* Appendix A, at 47-8.

2. FDA's Approved Regimen Is Not Restricted to Properly Trained Physicians who Have Admitting Privileges to Emergency Facilities

FDA's approved regimen lacks any objective qualifications for prescribing physicians and administering health care providers.²⁷³ The health care provider administering the Mifeprex Regime need not undergo training, may not necessarily be an obstetrician or gynecologist, may not have any surgical training or training in the management of abortion complications, and may not even be a physician.²⁷⁴ For example, the Mifeprex Regimen could be administered by a nurse untrained in any type of abortion and under the remote supervision of a family practitioner who does not regularly practice obstetrics and is incapable of providing emergency care.

Physicians and the health care staff that they supervise require formal training in both pharmaceutical and surgical abortion to minimize the morbidity inherent in performing mifepristone abortions.²⁷⁵ National Abortion Federation guidelines provide that "[a]ll personnel performing abortions must receive training in the performance of abortions and in the prevention,

²⁷³ Self-certifications do not provide an effective substitute for imposing objective, auditable requirements. The Mifeprex Prescriber's Agreement, for example, merely requires that the prescribing physician profess to have the "[a]bility to assess the duration of pregnancy accurately." The vacuity of this stipulation is illustrated in remarks made by Dr. Susan Allen (who later became an FDA official) before the FDA Advisory Committee. Dr. Allen stated, "If you also recall when you go through medical school you learn how to date a pregnancy." FDA Hearings Transcript, *infra* Appendix A, at 319.

²⁷⁴ See Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 ("the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners") [FDA FOIA Release: MIF 004587-88]; see also, Mifeprex Approval Memo, *infra* Appendix A, at 4-5 ("Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician from dispensing the drug to patients, provided state laws permit this.").

²⁷⁵ A survey of methotrexate abortion providers underscores the necessity of training in both medical and surgical abortion. See S. Marie Harvey, Linda J. Beckman, and Sarah J. Satre, "Experiences and Satisfaction with Providing Methotrexate-Induced Abortions among U.S. Providers," *Journal of the American Medical Women's Association* 55 (2000): 161-63, at 162 (In a study comparing methotrexate and surgical abortion, "[m]ost providers felt strongly that all clinic staff should be familiar with both procedures and, thus, the training needs would be equivalent. This thought was echoed not only by physicians, who must be prepared to perform an emergency surgical abortion if methotrexate fails, but also by other clinic personnel. Thirty-nine percent of providers thought that medical abortion

recognition, and management of complications.”²⁷⁶ Additionally, ACOG recommends that

“[c]linicians other than obstetrician-gynecologists who wish to provide medical abortion services should work in conjunction with an obstetrician-gynecologist or be trained in surgical abortion in order to offer medical abortion treatment.”²⁷⁷ The necessity for training in surgical abortion as

5 well as mifepristone abortion stems primarily from the high failure rate of the Mifeprex Regimen. In the U.S. Clinical Trial, the Mifeprex Regimen failed for 8 percent of women with pregnancies of less than or equal to 49 days’ gestational age.²⁷⁸

Excessive bleeding, which is much more common following a Mifeprex abortion than a surgical abortion, is particularly likely to necessitate urgent surgical intervention. Based on an

10 international study comparing surgical and medical abortion, FDA’s Medical Officer noted that “[o]n the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients” and characterized this as a “serious potential disadvantage of the medical method.”²⁷⁹ In the U.S. Clinical Trial among patients whose pregnancies were of no

15 more than 49 days’ gestation, excessive bleeding resulted in one blood transfusion, two hospitalizations, two emergency room treatments, and thirteen surgical interventions.²⁸⁰ In

required more training; specifically, learning to do a vaginal ultrasound and to handle the unpredictable outcomes of methotrexate abortion required lengthy training.”).

²⁷⁶ National Abortion Federation, “National Abortion Federation Clinical Policy Guidelines, 1998,” Appendix, in Maureen Paul et al., eds., *A Clinician’s Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999): at 256 (“*A Clinician’s Guide*”).

²⁷⁷ ACOG Practice Bulletin, *infra* Appendix A, at 6.

²⁷⁸ See Medical Officer’s Review, *infra* Appendix A, at Table 1. Seventeen percent of women with pregnancies of between 50 and 56 days’ gestational age and 23 percent of women with pregnancies between 56 and 63 days were failures. See *id.* In an international study reviewed by the Medical Officer, failure rates for mifepristone abortion were 5.2 percent, 8.6 percent and 16 percent in India, China and Cuba respectively, while comparable failure rates for surgical abortion were 0, 0.4 percent, and 4.0 percent. See Medical Officer’s Review, *infra* Appendix A, at 19.

²⁷⁹ Medical Officer’s Review, *infra* Appendix A, at 19 (no citation by FDA Medical Officer).

²⁸⁰ Medical Officer’s Review, *infra* Appendix A, at 17.

addition, 5 percent of the patients in this group received uterotonic agents to stem bleeding.²⁸¹ A delay in intervention may be life-threatening,²⁸² as was illustrated by the experience of one of the participants in the U.S. Clinical Trial. The treating physician described the incident to the FDA Advisory Committee:

5 In November of 1994, I was called to the [emergency room] for a woman who was bleeding due to a miscarriage, and was in obvious shock. A blood test showed that she had lost between one-half to two thirds of her blood volume . . .

I had thought she was having an incomplete miscarriage, but her husband . . . told me that she had taken RU486 approximately 2 weeks before. It was my clinical opinion
10 that she would die soon if she did not have an immediate [dilation and curettage].

Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.

15 Even later that evening, . . . [s]he required two more units of blood because she was still orthostatic and symptomatic.²⁸³

The Mifeprex Regimen is contraindicated for “any patient who does not have adequate access to medical facilities equipped to provide emergency treatment.”²⁸⁴ FDA’s approved
20 regimen, however, does not require prescribing physicians to have *admitting* privileges to emergency facilities. The approved regimen requires only that a physician who is not able “to provide surgical intervention in cases of incomplete abortion or severe bleeding . . . ma[k]e plans to provide such care through others, and [be] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.”²⁸⁵ Plans for back-up care

²⁸¹ Medical Officer’s Review, *infra* Appendix A, at 17.

²⁸² When surgery is indicated because of acute bleeding, significant, or even life threatening blood loss, has already taken place. The preoperative preparation of the patient is often compromised in the rush to complete the surgery, which results in higher infection rates and more anesthetic complications, such as aspiration during intubation.

²⁸³ FDA Hearings Transcript, *infra* Appendix A, at 223-25 (testimony of Dr. Mark Louviere).

²⁸⁴ See Mifeprex Label (“Contraindications”).

²⁸⁵ Mifeprex Prescriber’s Agreement. FDA, however, took two steps that suggested that it has lingering concerns about the absence of a surgical intervention qualification for Mifeprex prescribers. First, the Mifeprex Label includes a “black box” warning governing surgical back-up. Second, FDA required the Population Council to perform a post-approval study “[t]o ensure that the quality of care is not different for patients who are treated by

may be nothing more than “having the ability and responsibility to direct patients to hospitals, if needed.”²⁸⁶ Moreover, the approved regimen does not include an objective geographical limitation to ensure that the patient has easy access to the designated emergency care facility.²⁸⁷

3. The Sponsor’s Recent “Dear Doctor Letter” and FDA’s Explanatory Webpage Announcing Serious Adverse Events Validate the Petitioners’ Concerns

On April 17, 2002,²⁸⁸ Danco, with FDA’s assistance, issued a letter to health care providers to alert them to “New Safety Information,” to remind them that Mifeprex was approved for use in a prescribed regimen, and to encourage them to provide patient counseling and report adverse events.²⁸⁹ The “New Safety Information” consisted of a number of reports of serious adverse events that had been experienced by women who were undergoing or had

physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention . . .” Mifeprex Approval Memo, *infra* Appendix A, at 5.

²⁸⁶ Mifeprex Approval Memo, *infra* Appendix A, at 5. FDA’s decision not to include a requirement that the prescribing physician have admitting privileges at a hospital could delay the patient’s admission for emergency care. Another likely consequence of not requiring the prescribing physician to have admitting privileges is underreporting of serious adverse events related to the Mifeprex Regimen. The treating physician, not privy to the Prescriber’s Agreement, may not file a serious adverse event report or notify the abortion provider of the complications that arose from the Mifeprex Regimen.

²⁸⁷ The Chinese experience with mifepristone suggests that mifepristone should not be administered in facilities unable to provide potentially necessary emergency services. Thus, recently, the Chinese State Drug Administration responded to concerns that women were suffering as a result of lax controls on mifepristone by reiterating its policy that the drug “can only be administered at a hospital under a doctor’s supervision and cannot be sold at pharmacies even with a prescription.” See Kaiser Family Foundation, “China Reaffirms Restrictions on Unsupervised Mifepristone Use,” *Kaiser Daily Reproductive Health Report* (Oct. 15, 2001) (available at: <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=7453>) (reporting also that, “[t]hree years ago, the Shanghai Health Bureau restricted the use of mifepristone to certain hospitals in the area because of fears of complications”).

²⁸⁸ The letter bears the date, April 19, 2002, but was disseminated to the public on April 17, 2002.

²⁸⁹ Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) (“Dear Doctor Letter”) (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>). Coincidentally, on the same day FDA and Danco publicized these serious adverse events, the agency also announced major changes to the Cytotec (misoprostol) label. See FDA, “Major Changes to Cytotec Labeling” (April 17, 2002). Pursuant to these labeling changes, pregnancy was removed from the list of contraindications on the Cytotec label and the black box warning cautioning pregnant women not to take the drug was also removed.

recently completed the Mifeprex Regimen.²⁹⁰ A number of patients had suffered from ruptured ectopic pregnancies and one of these women died from hemorrhage.²⁹¹ The letter also reported “[t]wo cases of serious systemic bacterial infection (one fatal).”²⁹² The fatality apparently precipitated a halt in the Population Council’s Canadian clinical trials of mifepristone.²⁹³ Finally, a 21 year old woman suffered a heart attack three days after she completed the Mifeprex Regimen.²⁹⁴ These and other adverse events had been reported to FDA through its Adverse Event Reporting System (AERS).²⁹⁵ Two of the patients who were reported to have suffered life-threatening adverse events were 15 years old.²⁹⁶ These incidents bear out the concerns about the safety of the regimen detailed above, and the relatively high rate of serious adverse events among adolescents is of particular concern.

²⁹⁰ The letter did not specify the number of adverse events about which Danco had been informed, but five individual cases were discussed.

²⁹¹ See Dear Doctor Letter, *infra* Appendix A, at 1.

²⁹² See Dear Doctor Letter, *infra* Appendix A, at 1.

²⁹³ It appears that the woman reported to have died from a systemic bacterial infection was a Canadian trial subject. See Marnie Ko, “A Volunteer Dies While Testing a Controversial New Drug, Bringing the Trial to a Halt,” The Report (Oct. 8, 2001) (available at: <<http://report.ca/archive/report/20011008/p48ai011008f.html>>). See also Henry P. Kaiser Family Foundation, “Population Council Announces Death of Woman Involved in Canadian Mifepristone/Misoprostol Trial,” Daily Reproductive Health Report (Sept. 11, 2001) (available at: <http://www.kaisernetwork.org/Daily_reports/rep_index.cfm?DR_ID=6877>). A *Clostridium sordellii* infection apparently caused the woman to suffer septic shock. See generally G.L. Mandell, J.E. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases* (5th ed. 2000): at 2551 (explaining that a disease process in which “clostridia clearly play a major pathogenic role i[s] uterine gas gangrene, now a rare complication that was previously seen in the setting of septic abortion.” “*C. sordellii* has been reported as a cause of uterine gas gangrene . . .”). See also FDA Q & A’s, *infra* Appendix A, at Question 3 (“Serious systemic bacterial infection is a severe life-threatening infection that spreads throughout the body and can cause death.”).

²⁹⁴ See Dear Doctor Letter, *infra* Appendix A, at 1.

²⁹⁵ See, e.g., Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3819498-2 (Nov. 2, 2001) (intervention to prevent permanent impairment or damage); 3806144-7 (Oct. 9, 2001) (death of a patient with an ectopic pregnancy); 3769840-6 (July 30, 2001) (hospitalization of patient with an ectopic pregnancy); 3769842-X (July 30, 2001) (intervention to prevent permanent impairment or damage); 3719885-7 (May 8, 2001) (death in conjunction with the use of misoprostol and Mifegyne, which is the trade name of mifepristone distributed in France); 3713452-7 (Apr. 27, 2001) (intervention to prevent permanent impairment or damage); and, 3769838-8 (July 30, 2001) (intervention to prevent permanent impairment or damage). The AERS depends on voluntary reporting and the accuracy of these reported adverse events cannot be verified, nor can the cause of these events be identified with certainty. There may have been other adverse events that were not reported.

Simultaneously with Danco's distribution of the *Dear Doctor Letter*, FDA published a webpage with 14 questions and answers related to mifepristone in an attempt to answer some of the questions likely to be prompted by the letter and to urge health care providers to adhere to the approved regimen.²⁹⁷ FDA's answers, however, leave much to be desired from a medical and scientific standpoint.

First, FDA has understated the possibility that the Mifeprex Regimen caused the serious adverse events reported in the letter.²⁹⁸ FDA did not adequately explain why women who were apparently healthy prior to undergoing the Mifeprex Regimen experienced life-threatening or fatal complications such as ruptured ectopic pregnancies, heart attacks, and systemic bacterial infections.

Second, FDA inappropriately attempted to link these adverse events to the unapproved vaginal administration of misoprostol.²⁹⁹ It was reckless for FDA to suggest that the vaginal administration of misoprostol caused these adverse events while overlooking critical flaws in the

²⁹⁶ See Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3803789-5 (Oct. 3, 2001) and 3815629-9 (Oct. 26, 2001).

²⁹⁷ FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") (available at: http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm).

²⁹⁸ See *Dear Doctor Letter*, *infra* Appendix A, at 1 ("No causal relationship between any of these events and use of Mifeprex and misoprostol has been established."). An FDA official interviewed (without attribution) downplayed the connection between the Mifeprex Regimen and the adverse events. See Susan Okie, "Physicians Sent Abortion Pill Alert: Six Women Using RU-486 Taken Ill, and Two Died, Letter Says," *Washington Post* (Apr. 18, 2002): at A2 ("These are, in fact, a very small number of events. Some of them were clearly not caused by the drug regimen.").

²⁹⁹ The repeated references to the unapproved vaginal use of misoprostol in the FDA Q & As give rise to the inference that the reported adverse events are attributable to this single departure from the Mifeprex Regimen. See, e.g., FDA Q & As, *infra* Appendix A, at Question 1 ("In all of these cases, misoprostol was given vaginally, not orally, which is the approved regimen. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol."); *id.* at Question 4 ("We do not know what role, if any, Mifeprex and 'off-label' use of vaginal misoprostol may have in developing serious infections."); *id.* at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses? There are published studies of the use of mifepristone with vaginal administration of misoprostol for abortion. The misoprostol doses used in these studies are higher than those described in the Mifeprex labeling . . ."); *id.* at Question 10 ("Are there risks with vaginal use of misoprostol?").

approved regimen for Mifeprex use in the United States. FDA should have first assessed essential aspects of this regimen.

It is clear, for example, that absent ultrasonographic screening for ectopic pregnancy, there is increased risk that an intact or rupturing ectopic pregnancy will be misdiagnosed as a normally progressing Mifeprex abortion. Additionally, Mifeprex abortions may be performed by practitioners who are not physicians, who cannot perform surgical abortions, or who are unable to diagnose ectopic pregnancies and their complications.

Nor is there reason to believe that systemic bacterial infection is more likely to occur following vaginal, rather than oral, administration of misoprostol. Misoprostol is commonly administered vaginally for the induction of labor without higher reported rates of either intrauterine or systemic infection when compared to orally administered misoprostol or other methods of labor induction. Rather, the occurrence of life-threatening infection in women undergoing a Mifeprex abortion should raise questions about whether prolonged genital tract bleeding in the artificial hormonal milieu created by the Mifeprex Regimen might foster or promote infectious complications. In addition, infection might occur in women who, believing that their abortion is complete and unaware that their uterus actually contains dead tissue, fail to return for follow-up visits.³⁰⁰ This may be a particular problem when the Mifeprex Regimen is prescribed to adolescents.

The occurrence of a heart attack in a 21 year old woman is always cause for significant concern. A French woman undergoing a mifepristone abortion suffered a fatal heart attack in

³⁰⁰ A. Karen Kreutner, M.D., "Postabortion Infections," *Contemporary Ob/Gyn* 1 (2001): at 37-42 ("... because medical termination may be incomplete in between 3% and 23% of patients, retained tissue and subsequent infection may go unrecognized in those lost to follow up. ... Some experts fear there will be compliance problems with the third visit, especially when the patient terminates early. In these cases, retained tissue, thought by the patient to be normal bleeding, could lead to endometritis.").

1991. A different prostaglandin (Sulprostone) administered by injection was used in that case.³⁰¹

This new case highlights the need for further investigation into a possible causal link between mifepristone-prostaglandin abortions and myocardial infarction.³⁰²

The ratio of serious adverse events to total uses of the Mifeprex Regimen cannot be
 5 ascertained because serious adverse event reporting is likely incomplete and because it is not
 publicly known how many times the Mifeprex Regimen has been used. Regardless of the
 relative number of serious adverse events, the nature of these events demands immediate FDA
 action to prevent future patient injuries and deaths.³⁰³ The Joint Commission on the
 Accreditation of Healthcare Organizations³⁰⁴ (“JCAHO” or “Joint Commission”) has developed
 10 an approach for investigating adverse events similar in gravity to those that prompted the
 issuance of the Dear Doctor Letter. The JCAHO looks for “sentinel events” which are
 “unexpected occurrence[s] involving death or serious physical or psychological injury, or the
 risk thereof.”³⁰⁵ “Sentinel events” *signal* the need for the commencement of a “root cause

³⁰¹ See “Noticeboard: A Death Associated with Mifepristone/Sulprostone,” *Lancet* 337 (April 20, 1991): at 969-70 (“A spokeswoman for Roussel-Uclaf SA, the company that manufactures mifepristone, said ‘the death was clearly from cardiovascular shock following ‘Nalador’ (Schering) injection.’”).

³⁰² The Mifeprex Regimen should be contraindicated for women with cardiovascular risk factors until further clinical experience indicates that such contraindication is unnecessary.

³⁰³ Even FDA acknowledged the rarity of the events referenced in the Dear Doctor Letter. With respect to bacterial infection, for example, FDA observed that “the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1-4.7% of first trimester surgical abortions and in 0.0-6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth.” FDA Q & A’s, *infra* Appendix A, at Question 3. FDA similarly noted the unusual nature of a heart attack in a young woman: “The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare. . . . In 1997, the rate among US women aged 20-24 years was 0.19 per 100,000 women.” See *id.* at Question 4.

³⁰⁴ The Joint Commission “evaluates and accredits nearly 18,000 health care organizations and programs in the United States. An independent, not-for-profit organization, JCAHO is the nation’s predominant standards-setting and accrediting body in health care. Since 1951, JCAHO has developed state-of-the-art, professionally based standards and evaluated the compliance of health care organizations against these benchmarks.” Joint Commission webpage at: <http://www.jcaho.org/whatwedo_frm.html>.

³⁰⁵ Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#I. Sentinel Events>.

analysis” of the event(s),³⁰⁶ with the goal of developing an appropriate administrative response from the health care organization that will prevent the occurrence of future serious adverse events. A root cause analysis of sentinel events is performed before a statistically significant number of injuries or deaths occurs. It seeks to discern the facts surrounding each occurrence, distinguish factors peculiar to individuals from those pointing to procedural or administrative deficiencies, and recommend corrective measures to such systemic failures in the delivery of a particular therapy.

It is particularly important that FDA react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA’s endorsed scientific methodology for such trials. The substandard trial design of the U.S. and French Clinical Trials precluded an accurate estimation of the safety of the Mifeprex Regimen compared to the existing available alternatives. Moreover, FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data. The agency has not performed a root cause analysis, but has instead hastily postulated that the vaginal administration of misoprostol is the underlying cause of the adverse events.³⁰⁷ The Petitioners believe that there are probably more scientifically sound explanations for these adverse events and that the supposed safety of the Mifeprex Regimen has been called into question. The occurrence of the adverse events related to ectopic pregnancies and life-threatening systemic bacterial infections adds significant weight to the concerns of those

³⁰⁶ The Joint Commission defines “root cause analysis” as “a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event. A root cause analysis focuses primarily on systems and processes, not individual performance. It progresses from special causes in clinical processes to common causes in organizational processes and identifies potential improvements in processes or systems that would tend to decrease the likelihood of such events in the future, or determines, after analysis, that no such improvement opportunities exist.” Joint Commission webpage at: <[http://www.jcaho.org/sentinel/se_pp.html#Root cause analysis](http://www.jcaho.org/sentinel/se_pp.html#Root%20cause%20analysis)>.

who have long warned that mifepristone-misoprostol abortions are dangerous. FDA has previously dismissed such concerns but now must respond to the accumulating evidence and act accordingly. Withdrawal of the approval is warranted.³⁰⁸

5 **H. FDA'S APPROVAL OF MIFEPREX SHOULD BE WITHDRAWN
BECAUSE THE SPONSOR IS NOT ENFORCING THE LIMITED
RESTRICTIONS ON THE USE OF MIFEPREX**

Mifeprex abortion providers openly flout the restrictions included in the approved
10 regimen without any reaction from FDA, Danco, or the Population Council.³⁰⁹ Shortly after
approval, FDA asserted that “[i]f restrictions are not adhered to, FDA may withdraw
approval.”³¹⁰ Subpart H authorizes FDA to withdraw approval of a drug approved under Section
314.520 if “[t]he applicant fails to adhere to the postmarketing restrictions agreed upon.”³¹¹

When it adopted Subpart H, FDA explained that “[t]he burden is on the applicant to ensure that

³⁰⁷ See FDA Q & As, *infra* Appendix A, at Nos. 1, 4, 9, 10, and 11.

³⁰⁸ The Secretary of HHS is authorized by 21 C.F.R. § 314.530(a) to withdraw approval of a Subpart H drug, subject to the applicant's right to a hearing, if, among other things, “(3) [u]se after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug; (4) [t]he applicant fails to adhere to the postmarketing restrictions agreed upon; (5) [t]he promotional materials are false or misleading; or (6) [o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.”

³⁰⁹ The absence of a reaction from Danco may not be surprising in light of the cavalier attitude towards the FDA approval process exhibited by Dr. Richard Hausknecht, who is Danco's medical director. As early as July 1994, Dr. Hausknecht, had used methotrexate and misoprostol in clinical tests in the U.S. that Dr. Mitchell Creinin, a prominent abortion researcher, described as “downright unethical” and which Sandra Waldman of the Population Council described as being “very risky.” Dr. Hausknecht stopped these experiments in September 1994 when the FDA told him to “stop performing the abortions unless he gets the backing of a medical institution and submits his data and procedures to the FDA for review.” Carol Jouzaitis, “Doctor's Abortion-Drug Technique Draws Fire,” *Chicago Tribune* (Sept. 12, 1994): at 1 & 14. Dr. Hausknecht admitted, “‘This is a little bit uncharted.’ But he declared: ‘Damn it. I'm not going to wait. This is a step forward. This is important. I want to see this available to women where it's not available now.’” *Id.* In addition, Dr. Hausknecht's website explains step two of the Mifeprex procedure that he employs: “At the conclusion of the [first] visit, the patient receives a packet containing tablets of misoprostol which are to be taken orally or placed in the vagina depending on the regimen you and Dr. Hausknecht choose.” Available at: <<http://www.safeabortion.com/procedure.htm>> (visited July 7, 2002). Both the home use and the vaginal administration of misoprostol contravene FDA's approved regimen.

³¹⁰ See Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

³¹¹ 21 C.F.R. § 314.530(a)(4).

the conditions of use under which the applicant's product was approved are being followed."³¹²

FDA should exercise its authority to withdraw its approval for Mifeprex.

Among the common departures from the approved regimen is the practice of offering the Regimen to women with pregnancies beyond seven weeks.³¹³ The "Mifepristone Medication Guide" directs women not to take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began." Moreover, women who use the Mifeprex Regimen sign a Patient Agreement, which includes a representation by the patient that "I believe I am no more than 49 days (7 weeks) pregnant."³¹⁴ Thus, the practice of offering Mifeprex to women beyond seven weeks not only contravenes the approved regimen, but it also effectively requires patients to make an untruthful representation in the Patient Agreement. The *Los Angeles Times* explained that, "[B]y offering mifepristone up to the ninth week of pregnancy," Family Planning Associates, "the nation's largest for-profit abortion chain," "obtains a competitive edge over Planned Parenthood, which stays within the seven-week guideline."³¹⁵

In another common deviation from the approved regimen, some abortion providers have eliminated the second of the three prescribed visits. During the initial visit, these providers give

³¹² *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

³¹³ Liberty Women's Health Care of Queens, NY, openly acknowledges its use of Mifeprex beyond seven weeks: "While the FDA has approved mifepristone for non-surgical abortions only up to 7 weeks, we use a modified method to extend this period of eligibility in selected patients an additional 14 days up to 9 weeks." Available at: <<http://www.abortbypill.com/2.html>> (visited Dec. 31, 2001). Likewise, Preterm, an abortion clinic in Cleveland, Ohio, states that abortion using Mifeprex "is effective in terminating pregnancies up to 63 days (9 weeks) from the last normal menstrual period." Available at: <<http://www.preterm.org/nonsurg.htm>> (visited July 7, 2002).

³¹⁴ See Item 4 of the Patient Agreement for Mifeprex (mifepristone) Tablets ("Patient Agreement").

³¹⁵ Denise Gellene, "RU-486 Abortion Pill Hasn't Caught on in U.S.," *Los Angeles Times* (May 31, 2000): at A1 (quoting Family Planning Associates' official as saying, "You can catch a lot of women in those two [extra] weeks"). Family Planning Associates' website confirmed that the abortion provider offers Mifeprex to women with pregnancies up to nine weeks' gestational age. Available at: <http://www.webworldinc.com/fpamg/abortion_pill.htm> (visited July 7, 2002) ("Medical abortion is limited to patients less than nine weeks pregnant as verified by ultrasound").

the patient misoprostol, typically with instructions to administer it to herself vaginally³¹⁶ at home two days later.³¹⁷ Yet home administration of misoprostol runs counter to what patients agree to in the Patient Agreement, which states that “I will . . . return to my provider’s office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.”³¹⁸ The Population Council argued in favor of and FDA considered the benefits of self-administration at home, chief among which is the reduced burden on abortion providers and their facilities, but the agency concluded that these benefits are outweighed by the significant risks to women.³¹⁹ The second visit affords the physician the opportunity to monitor the status of

³¹⁶ The likely reason that FDA’s approved regimen calls for oral administration is that it is the only mode of administering misoprostol that is currently approved by the FDA. As discussed above, however, the use of misoprostol in conjunction with mifepristone to effect abortions is itself an unapproved indication.

³¹⁷ Presidential Women’s Center in West Palm Beach, Florida, for example, gives women “four Misoprostol 200 mcg tablets to take home. Forty eight hours after the Mifepristone tablets have been administered the woman moistens four Misoprostol tablets with tap water and inserts them high into her vagina with her fingers.” Available at: <<http://www.presidentialcenter.com/medical.html>> (visited July 7, 2002). *See also*: <http://www.heritageclinic.com/abortion/medical_abortion_pill.htm> (visited July 4, 2002) (Two days after the patient takes mifepristone, she “inserts Cytotec vaginally, which causes the uterus to contract and expel the embryo. This is very similar to the procedure that was FDA approved in 2000 and is approximately 98% effective. **Note:** The FDA approved protocol calls for 3 Mifeprex pills taken orally the first day and 2 Cytotec pills taken orally two days later. However, subsequent studies have show[n] 1 oral Mifeprex and 4 vaginal Cytotec to be as effective with less gastro-intestinal upset.”); *see also*: <<http://www.fwhc.org/concord/pages/mifepristone.html>> (visited July 7, 2002) (Concord Feminist Health Center’s web site describes the second phase of the procedure: “In a few days she inserts misoprostol tablets into her vagina. The pregnancy usually ends at home within four hours.”); *see also*: <<http://www.gynemed.org/ru.html>> (visited July 7, 2002) (Gynemed Surgi-Center’s web site states: “You will be given two doses of Misoprostol tablets and instructions on how to insert them into your vagina, which you wil[l] do 48 hours after taking RU486.”); *see also*: <<http://www.hopeclinic.com/medab.htm>> (visited July 7, 2002) (Hope Clinic for Women, Ltd. Explains: “You will receive pills, misoprostol (“miss o pross tul”) to take home with you. You will be instructed when to use them; they are placed vaginally.”). Even the National Abortion Federation, which initiated a nationwide advertising campaign for Mifeprex, sanctions home administration of misoprostol in its “Medical Abortion Start-Up Packet.” *See* National Abortion Federation, “Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion,” *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 36 (“Home administration of vaginal misoprostol has been found to be safe and effective up to 63 days’ gestation and is highly acceptable to patients.”).

³¹⁸ *See* Patient Agreement, Item 14. *See also* Mifeprex Medication Guide, which explains that on “Day 3 at your provider’s office,” “your provider will check to see if you are still pregnant,” and “[i]f you are still pregnant, take 2 misoprostol tablets.”

³¹⁹ FDA, which in its 2000 Mifepristone Approvable Letter, agreed to the Population Council’s proposal to allow home administration of misoprostol, rejected that option after reconsideration of the issue. *See* Mifeprex Approval Memo, *infra* Appendix A, at 2-3 (“The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council’s statement that women could have the option of taking misoprostol on Day 3 either at home or at the

the termination³²⁰ and assess the need for misoprostol – tasks which cannot be delegated to the patient.³²¹ In addition, the second visit enables patients whose abortions are complete to avoid having to take misoprostol.³²²

Danco and the Population Council have not effectively constrained providers of Mifeprex to adhere to the approved regimen. It appears instead that Danco and the Population Council have ignored well-publicized departures from that regimen. Deviations from the approved regimen are particularly troubling because the patient is told to disregard the regimen that she reads about in the Medication Guide and pledges to follow in the Patient Agreement. When a drug is approved under Subpart H, the drug's sponsor is responsible for ensuring compliance

prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. . . . Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.”).

³²⁰ Because of the complications that can arise, periodic monitoring during the termination process is important. For the significant percentage of patients that fail to return for the third visit, the second visit may be the last opportunity for a health care provider to monitor the termination. In the U.S. Clinical Trial, five percent of patients failed to return for the third visit. See Medical Officer's Review, *infra* Appendix A, at 10. In other studies, the “loss to follow-up has ranged from three to eleven percent.” See Spitz Article, *infra* Appendix A, at 1246 (citations omitted). The rate of patients who do not complete the entire regimen in routine clinical practice is likely to be even higher as they will not necessarily be subject to the U.S. Clinical Trial's exclusion criteria, which, among other things, excluded women who were “unlikely to understand and comply with the requirements of the study.” Medical Officer's Review, *infra* Appendix A, at 9.

³²¹ See ACOG Practice Bulletin, *infra* Appendix A, at 6 (citing Mitchell Creinin, *et al.*, “Methotrexate and Misoprostol for Early Abortion: A Multicenter Trial,” *Contraception* 53 (1996): at 321-27) (“Women as well as their practitioners are often unable to judge correctly if the women have aborted by evaluating symptomatology. In clinical trials with methotrexate and misoprostol, only about half of women who thought they had aborted actually had done so.”); Beth Kruse *et al.*, “Management of Side Effects and Complications in Medical Abortion,” *American Journal of Obstetrics and Gynecology* 183 (2000): S65-375, S73 (“Studies demonstrate that women may be unable to judge correctly on the basis of symptoms whether abortion has occurred.”).

³²² For those patients whose abortions are not complete, the benefits of in-clinic misoprostol use would be enhanced if patients were required to spend several hours afterward in the abortion facility, where they would have ready access to pain medication and other medical help even if the abortion does not occur during the observation period. The Population Council persuaded FDA not to include this requirement, which was included in the protocol for the U.S. Clinical Trial. Forty-nine percent of the participants expelled their pregnancies during the four-hour observation period after the administration of misoprostol. See Spitz Article, *infra* Appendix A, at 1243. Nevertheless, a post-misoprostol waiting period was likely disfavored because the protracted presence of large numbers of bleeding and cramping women could place a strain on abortion facilities.

with the restrictions included in the approved regimen for use of the drug.³²³ The Population Council and Danco have shirked this responsibility. FDA, therefore, should withdraw its approval of Mifeprex.

5 **I. THE U.S. CLINICAL TRIAL FOR MIFEPRISTONE DID NOT MIRROR THE ANTICIPATED CONDITIONS FOR THE ULTIMATE USE OF THE DRUG**

As a general rule, “Phase 3 trials are usually [conducted] in settings similar to those anticipated for the ultimate use of the drug.”³²⁴ FDA, however, approved a regimen that does not contain important safeguards that were employed in the U.S. Clinical Trial.³²⁵ In the U.S. Clinical Trial, for example, the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy.³²⁶ The use of ultrasonography also excluded women with ectopic pregnancies. Moreover, physicians participating in the U.S. Clinical Trial had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization.³²⁷ In addition, “[a]ll patients were within one hour of emergency facilities or the

³²³ See *Subpart H Final Rule*, 57 Fed. Reg. at 58953 (“The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant’s product was approved are being followed.”).

³²⁴ Bertram G. Katzung, M.D., Ph.D., and Barry A. Berkowitz, Ph.D., “Basic & Clinical Evaluation of New Drugs” in Bertram G. Katzung, ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk: Appleton & Lange, 1989): at 56.

³²⁵ The French Clinical Trials, which were not performed by the Population Council, are not discussed here because they were not conducted for the purpose of supporting the mifepristone NDA and, therefore, were not designed to reflect American conditions of use.

³²⁶ See Spitz Article, *infra* Appendix A, at 1242.

³²⁷ “The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and /or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists.” Mifeprex Approval Memo, *infra* Appendix A, at 5. Medical Officer’s Review,

facilities of the principle [*sic*] investigator.”³²⁸ In the U.S. Clinical Trial, after taking misoprostol, “women were monitored for four hours for adverse events.”³²⁹ FDA has not retained these requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care.³³⁰ FDA should not have extrapolated conclusions about the safety and efficacy of FDA’s approved regimen from data generated under trial conditions not mirroring the approved regimen. Effectively, therefore, the agency approved a drug regimen that it had not tested.

J. BY WAIVING THE PEDIATRIC STUDY REQUIREMENT, FDA MAY HAVE ENDANGERED THE HEALTH OF ADOLESCENT GIRLS

FDA’s approval of Mifeprex violated FDA’s regulations, effective April 1, 1999, requiring that new drugs be tested for safety and effectiveness in the pediatric population (collectively, the “*Pediatric Rule*”).³³¹ Requiring data on girls age 18 and under also would have been consistent with the guidelines for trials in the pediatric population that FDA accepted at the

infra Appendix A, at 6 (The U.S. Clinical Trial was “conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.”).

³²⁸ Mifeprex Approval Memo, *infra* Appendix A, at 5. The “one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services.” *Id.* FDA contends that concerns arising from the elimination of the geographical proximity rule have “been dealt with through labeling, which makes it clear that if there isn’t adequate access to emergency services, the medication is contraindicated.” Mifeprex Approval Memo at 5.

³²⁹ See Spitz Study, *infra* Appendix A, at 1242.

³³⁰ The Prescriber’s Agreement requires only that the supervising physician be “able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.” By contrast, the protocol for the U.S. Clinical Trial required that the physician have “privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc.” Mifeprex Approval Memo, *infra* Appendix A, at 5. The shift in focus from access by the provider of the abortion to access by the woman who has the abortion, attenuated the link between the abortion provider and the emergency care provider, a link that is critical to ensuring that women receive timely emergency care.

³³¹ See Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (*Pediatric Adopting Release*). The notice of proposed rulemaking was released as: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Proposed Rule*, 62 Fed. Reg. 43900 (Aug. 15, 1997).

International Conference on Harmonization.³³² Nevertheless, in the Mifeprex Approval Letter, FDA stated, “We are waiving the pediatric study requirement for this action on this application.”³³³ Thus, FDA approved Mifeprex for use without requiring safety and effectiveness testing for the pediatric population.³³⁴

5 As FDA noted when it adopted the *Pediatric Rule*, “many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established.”³³⁵ FDA observed that “the absence of pediatric labeling information poses significant risks for children.”³³⁶ The ICH has noted that adolescence “is a period of sexual maturation; medicinal products may interfere with the actions
10 of sex hormones and impede development.”³³⁷ Such hormonal changes may “influence the results of clinical studies.”³³⁸ These concerns for the health of infants, children, and adolescents

³³² *FDA Guidance: E11 Clinical Testing for Pediatric Uses* at 9 and 11 (Heading for Section 2.5.5). FDA, cognizant of the need for such studies, obtained a commitment from the sponsor in 1996 to conduct Phase IV studies to examine the safety and efficacy of the regimen in girls under 18 years of age. FDA subsequently curtailed this Phase IV study requirement when it approved the Mifeprex NDA.

³³³ Mifeprex Approval Letter at 3.

³³⁴ The Mifeprex Label accordingly included the standard disclaimer employed in drug labeling when the drug sponsor has not provided sufficient information to support a pediatric use for the drug: “Safety and effectiveness in pediatric patients have not been established.”

³³⁵ *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

³³⁶ *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

³³⁷ FDA, “Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population” (Rockville, Md.: Dec. 2000): at 11 (§ 2.5.5) (“*FDA Guidance: E11 Clinical Testing for Pediatric Uses*”). Section 2.5.5 states that the adolescent subgroup should extend from “12 to 16-18 years (dependent on region).” *Id.* at 11-12 (§ 2.5.5).

³³⁸ See *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 12 (§ 2.5.5). These ICH concerns, quoted below, pertaining to the difficulty of testing drugs in the adolescent population amplify the need for FDA to have required clinical study of the difficulties that might arise when teenage girls undergo the Mifeprex Regimen:

Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect

prompted FDA to begin the rulemaking that culminated with the issuance of the *Pediatric Rule*, establishing “a presumption that all new drugs and biologics will be studied in pediatric patients” unless the requirement is waived.³³⁹ More specifically, the *Pediatric Rule* requires that applicants seeking approval for new chemical entities, new biological products, new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration contain safety and effectiveness information on relevant pediatric age groups.³⁴⁰

FDA made clear that the Mifeprex NDA was covered by the *Pediatric Rule*.³⁴¹

Nevertheless, FDA fully waived the rule for Mifeprex without explanation. Full or partial

appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol, and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.”).

Id. at 12 (§ 2.5.5).

³³⁹ *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 (introduction to “II. Highlights of the Final Rule”). The importance of testing drugs in children was highlighted during the recent controversy surrounding FDA’s attempt to suspend the *Pediatric Rule*. FDA’s planned two-year suspension came in response to the passage of the Best Pharmaceuticals for Children Act, which offers incentives for manufacturers to test drugs in children. Public Law No. 107-109, 115 Stat. 1408 (“BPCA”). See also *Association of American Physicians and Surgeons, Inc. v. FDA*, Defendants’ Motion for Stay of Proceedings, Civil Action No. 00-2898 (HHK) (Mar. 18, 2002). FDA later reversed its position in response to criticism from physicians and members of Congress. FDA’s attempt to suspend the *Pediatric Rule* prompted the introduction of identical legislation in the House of Representatives and the Senate to codify the *Pediatric Rule*. See S. 2394, 107th Congress, 2nd Session (2002) (co-sponsors: Senators Hillary Rodham Clinton (D-NY), Mike DeWine (R-OH), and Chris Dodd (D-CT)); and H.R. 4730, 107th Congress, 2nd Session (2002) (co-sponsors: Representatives John D. Dingell (D-MI), Henry A. Waxman (D-CA), Rosa DeLauro (D-CT), Anna Eshoo (D-CA) and Sherrod Brown (D-OH)). As Senator Hillary Rodham Clinton, a co-sponsor of the Senate bill explained, “if we want to protect our children over the long term, then we in Congress need to step in and make the Pediatric Rule the law of the land. Short of taking that action, we risk denying children the protection that we require for adults.” Press Release, “Senators Will Introduce Legislation to Codify Pediatric Rule” (Apr. 17, 2002) (available at: <<http://clinton.senate.gov/~clinton/news/2002/04/2002417811.html>>). See also Marc Kaufman and Ceci Connolly, “U.S. Backs Pediatric Tests In Reversal on Drug Safety,” *Washington Post* (April 20, 2002): at A3.

³⁴⁰ *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 (“A. Scope of the Rule”), and as required pursuant to 21 C.F.R. § 314.55(a).

³⁴¹ The Mifeprex Approval Letter stated: “Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.” Mifeprex Approval Letter at 3. Because the Mifeprex NDA was filed before the Pediatric Rule went

waivers of the pediatric study requirement may be granted either upon request of the applicant or by FDA on its own motion.³⁴² Both FDA-initiated and sponsor-requested waivers must satisfy certain criteria. FDA is required to grant a full or partial waiver “if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver ... have been met.”³⁴³

Section 314.55 provides three procedural tracks by which an applicant may obtain a waiver of the study requirement. The first requires that two conditions being met:³⁴⁴ (1) “[t]he drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients,” and (2) the drug product “is not likely to be used in a substantial number of pediatric patients.” With respect to this basis for waiver, FDA has “emphasize[d] that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa.”³⁴⁵ As noted above, FDA, in connection with its determination to approve Mifeprex under Subpart H, concluded that the Mifeprex Regimen provides a therapeutic benefit over the existing treatment – surgical

into effect, if a waiver had not been granted, the Population Council would have had until December 2, 2000 to submit “an assessment of pediatric safety and effectiveness.” See *Pediatric Adopting Release*, 63 Fed. Reg. at 66658-59 (“V. Implementation Plan”).

³⁴² Although it appears that FDA waived the rule *sua sponte*, FDA should have required the manufacturer to provide certain information to support the waiver. The agency has not released such documents to the public in response to FOIA requests. When it adopted the *Pediatric Rule*, the agency noted: “FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request.” *Pediatric Adopting Release*, 63 Fed. Reg. at 66648 (§ 29).

³⁴³ 21 C.F.R. § 314.55(c)(4) (“FDA action on waiver.”).

³⁴⁴ 21 C.F.R. § 314.55(c)(2)(i).

³⁴⁵ *Pediatric Adopting Release*, 63 Fed. Reg. at 66635 (“II.D.2. Waiver of the Study Requirement,” see first paragraph).

abortion.³⁴⁶ This conclusion by itself precludes FDA from using the first method for granting waiver of the *Pediatric Rule*.³⁴⁷

Even if FDA had not judged the Mifeprex Regimen to offer a “meaningful therapeutic benefit,” the second requirement for waiver in this first track is not met because Mifeprex can be expected to be used in a “substantial number of pediatric patients,” which FDA defines as “50,000 pediatric patients with the disease for which the drug or biological product is indicated.”³⁴⁸ In the *Pediatric Adopting Release*, FDA stated that the “relevant age groups will . . . be defined flexibly.”³⁴⁹ With respect to Mifeprex, it would have been appropriate to classify girls under the age of 18 as pediatric patients because safety and effectiveness in this population had not been studied.³⁵⁰ If the pediatric population comprises all girls age 17 and under, then we estimate that there were 357,200 pediatric pregnancies per year from 1995 to 1997 in the United States.³⁵¹ If the pediatric population comprises all girls age 16 and under, then we estimate that there were a total of 196,520 pregnancies per year from 1995 to 1997.³⁵² Even if the pediatric population encompasses only girls age 15 and under, we estimate that there were

³⁴⁶ See Mifeprex Approval Memo at 6.

³⁴⁷ FDA noted that, for purposes of the *Pediatric Rule*, it would rely “in part, on CDER’s current administrative definition of a ‘Priority’ drug, applied to pediatric populations” to define “meaningful therapeutic benefit.” The phrase, “meaningful therapeutic benefit,” appears identical in the Subpart H and Priority review contexts. As noted above, Mifeprex was accorded priority review. The modifications to “meaningful therapeutic benefit” for purposes of the *Pediatric Rule* appear to have broadened the scope of the phrase. See *Pediatric Rule*, 63 Fed. Reg. at 66646.

³⁴⁸ *Pediatric Adopting Release*, 63 Fed. Reg. at 66647.

³⁴⁹ *Pediatric Rule*, 63 Fed. Reg. at 66634 (“C. Age Groups”). After noting comments to the proposed rule that argued for flexibility in setting age definitions (including a comment arguing for “pediatric patient” to include those “from 0 to 21 years”), FDA stated that “the age ranges identified in the proposal may be inappropriate in some instances” and that it had “deleted the references in the rule to specific age ranges.” *Id.* at 66651.

³⁵⁰ Although FDA acknowledged that the safety and effectiveness of Mifeprex were not studied in girls under age 18 and required a statement to that effect in the labeling, the agency anticipated and even encouraged use in this population when it stated that: “there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients.” Mifeprex Approval Memo at 7.

³⁵¹ See *infra* Appendix B at B-3.

³⁵² See *infra* Appendix B at B-4.

85,960 pregnancies per year from 1995 to 1997 in this age range.³⁵³ Thus, under any definition of the pediatric population, the 50,000 patient cut-off set forth in the *Pediatric Adopting Release* is exceeded. In sum, *neither* of the requisite conditions for a waiver of the *Pediatric Rule* under the first waiver track provided in Section 314.55 is satisfied.³⁵⁴

5 Second, FDA may also waive the pediatric study requirements if the “necessary studies are impossible or highly impractical because, *e.g.*, the number of such patients is so small or geographically dispersed.”³⁵⁵ FDA explained that “that this ground for waiver [must] be interpreted narrowly”.³⁵⁶

10 Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. . . . Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.³⁵⁷

15 Pediatric Mifeprex studies would not have been either “impossible or highly impractical.” As described above and in Appendix B, the population of pediatric females that becomes pregnant each year is large and the female population is evenly distributed throughout the United States. Thus, this second waiver track available under Section 314.55 could not have been satisfied (and FDA apparently has not taken a position to the contrary).

20 FDA may waive the pediatric study requirement under Section 314.55’s third waiver track when “[t]here is evidence strongly suggesting that the drug product would be ineffective or

³⁵³ See *infra* Appendix B at B-4.

³⁵⁴ See 21 C.F.R. § 314.55(c)(2)(i).

³⁵⁵ See 21 C.F.R. § 314.55(c)(2)(ii).

³⁵⁶ *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

unsafe in all pediatric age groups.”³⁵⁸ As noted above, FDA endorsed the proposition that “there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen.”³⁵⁹ Thus, by suggesting that Mifeprex could be used appropriately in the pediatric population, FDA eliminated this third track as a possible basis for
 5 waiver.

Absent a waiver or deferral, the *Pediatric Rule* requires any drug application to “contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations”³⁶⁰ FDA is authorized instead to extrapolate such data from adult studies “[w]here the course of the disease and the effects of the
 10 drug are sufficiently similar in adults and pediatric patients.”³⁶¹ The underlying adult studies, however, must be “adequate and well-controlled.”³⁶² As noted above, the Population Council did not provide evidence from adequate and well-controlled studies as to the safety and effectiveness of Mifeprex in the *adult* population. Reliance on these flawed adult studies for a determination of the safety and effectiveness of Mifeprex in the pediatric population was inappropriate.

15 Furthermore, to assume that the effects of a potent antiprogesterone, mifepristone, and a

³⁵⁷ *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

³⁵⁸ 21 C.F.R. § 314.55(c)(2)(iii).

³⁵⁹ Mifeprex Approval Memo at 7.

³⁶⁰ 21 C.F.R. § 314.55(a). FDA stated that it was waiving the *Pediatric Rule*. Mifeprex Approval Letter at 3. The agency did not assert that it had made a determination that pediatric studies were not required because the adult trials were sufficient to support extrapolation of conclusions as to safety and effectiveness in the pediatric population. However, because FDA failed to provide any justification for its waiver, it is difficult to determine whether the agency was, in fact, relying on this provision to eliminate the pediatric study requirement for Mifeprex.

³⁶¹ See 21 C.F.R. § 314.55(a).

³⁶² See 21 C.F.R. § 314.55(a).

powerful prostaglandin analogue, misoprostol, in pregnant adults can be extrapolated to pregnant adolescents, who are still developing physiologically and anatomically, is medically unsound.³⁶³

FDA violated its own rules when it waived the Pediatric Rule in the face of explicit criteria that necessitated compliance with the rule.³⁶⁴ Furthermore, FDA offered no explanation

5 for its determination to waive the rule. As FDA's treatment of other drugs illustrates, a waiver would have been appropriate only if Mifeprex had already been tested in children and labeled accordingly, or if the *Pediatric Rule*'s criteria for waiver were satisfied.³⁶⁵ Because FDA waived

the study requirement in the face of explicit criteria that appear to prohibit such action in this

instance, the agency violated its rule. In addition to violating Section 314.55, FDA's

10 unexplained waiver of the *Pediatric Rule* for the Mifeprex NDA constitutes agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.³⁶⁶

³⁶³ The Mifeprex Regimen acts upon the reproductive system, which changes dramatically during adolescence. Adolescents, for example, could face disruptions in ovulatory function as a result of concentrations of mifepristone in developing ovarian follicles, or other health problems. Moreover, teenagers may face heightened risks arising from decreased compliance with the full regimen, poor recall of their last menstrual period, and their reluctance to tell others about their pregnancies.

³⁶⁴ Of course, a partial waiver of the study requirement is appropriate for the non-adolescent pediatric sub-groups. See 21 C.F.R. § 314.55(c)(3). According to *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses*, the pediatric sub-populations other than "adolescents" are: 1) preterm newborn infants; 2) term newborn infants (0 to 27 days); 3) infants and toddlers (28 days to 23 months); 4) children (2 to 11 years). *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 9 (§ 2.5).

³⁶⁵ In April 2000, FDA approved a suitability petition for Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials, and 9 mg/mL, 10 mL vials, the listed drug products for which are Aredia (Pamidronate Disodium for Injection), 30 mg/vial and 90 mg/vial, and determined that the "proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement . . . is appropriate." See Letter, FDA to Mitchell G. Clark (April 18, 2000): at 1 (Docket No. 00P-0091/CPI) (concluding "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed product in the pediatric population since the necessary studies are impossible or highly impractical because the number of patients is small and geographically dispersed"). See also Letter, FDA to The Weinberg Group, Inc. (June 13, 2000): at 1-2 (Docket No. 99P-5447/CPI) (approving a generic manufacturer's petition to file an Abbreviated New Drug Application for Cefaclor Chewable Tablets, 125 mg, 187 mg, 250 mg, and 375 mg, the listed drug products for which are Ceclor (Cefaclor) for Oral Suspension, 125 mg/5mL, 187 mg/5mL, 250 mg/5mL, and 375 mg/5mL because FDA determined that the "proposed change in dosage form is subject to the Pediatric Rule" but "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population, because the specific drug products that you reference are adequately labeled for pediatric use").

³⁶⁶ FDA has required numerous drug sponsors to comply with the *Pediatric Rule*, but it approved Mifeprex without stating its basis for waiving the requirement. See, e.g., Letter, FDA to King & Spalding (June 13, 2000): at 1

K. FDA'S UNEXPLAINED REDUCTION OF THE SPONSOR'S PHASE IV REQUIREMENTS WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

5 Not only did FDA improperly and without explanation waive its own pediatric testing requirements, but it also inexplicably narrowed the scope of the Population Council's commitments to conduct post-approval Phase IV studies. As a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and
10 effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects.³⁶⁷ Phase IV, which occurs after a drug is approved, provides the opportunity to "monitor[] the safety of the new drug under actual conditions of use in large numbers of patients."³⁶⁸ Not only

(Docket No. 99P-2776/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Oxycodone Hydrochloride and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL, the listed drug product for which is Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg, based on the fact that FDA "has determined that your proposed change in dosage form is subject to the Pediatric Rule and has concluded that investigations are necessary to demonstrate the safety and effectiveness in the pediatric population Therefore, the Agency concludes that the proposed product should be evaluated for safety and efficacy in the pediatric population."); Letter, FDA to Abbott Laboratories (Sept. 29, 1999): at 1-2 (Docket No. 98P-0821/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Hydromorphone Hydrochloride Injection, 0.2 mg/mL, 30 mL vials, the listed drug product for which is Dilaudid-HP Injection, 10 mg/mL, 5 mL ampoules and 50 mL vials, because the "proposed change in route of administration is subject to the Pediatric Rule," "clinical trials are required for this specific drug product," and "investigations are necessary to demonstrate the safety and effectiveness in the pediatric population").

³⁶⁷ A.G. Gilman, T.W. Rall, A.S. Nies, P. Taylor, eds., *The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990): at 77 ("Although assessment of risk is a major objective of [clinical trials], this is far more difficult than is the determination of whether a drug is efficacious for a selected condition. Usually about 500 to 300 carefully selected patients receive a new drug during phase-3 clinical trials Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly.").

³⁶⁸ Bertram G. Katzung, M.D., ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk, CT: Appleton & Lange, 1989): at 56. "Final release of a drug for general prescription use should be accompanied by a vigilant postmarketing surveillance program. The importance of careful and complete reporting of toxicity after marketing approval by the FDA can be appreciated by noting that many drug-induced effects have an incidence of 1:10,000 or less. . . . Because of the small numbers of subjects in phases 1-3, such low-incidence drug effects will not generally be detected before Phase 4, no matter how carefully the studies are executed. Phase 4 has no fixed duration." *Id.* at 56-7.

did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the Phase IV trials that it would perform.

5 In response to an FDA request, on September 16, 1996, the Population Council agreed to conduct a set of Phase IV studies.³⁶⁹ FDA “reminded” the Population Council of these commitments in both the 1996 and 2000 Approvable Letters.³⁷⁰ The Population Council agreed to perform studies with the following objectives:

- 10 1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
- 15 5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect on children born after treatment failure.³⁷¹

These studies would have addressed some of the health issues that were not evaluated during pre-approval testing.

20 The Mifeprex Approval Letter released on September 28, 2000, however, contains only two Phase 4 study obligations, a radical curtailment of the earlier commitments.³⁷² The letter

³⁶⁹ FDA made its request on August 22, 1996, after it had received Phase IV study recommendations from the FDA Advisory Committee. See Medical Officer’s Review, *infra* Appendix A, at 20-24.

³⁷⁰ See 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

³⁷¹ 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

³⁷² See Mifeprex Approval Letter, *infra* Appendix A, at 2-3.

stated that “the following Phase 4 commitments, specified in [the Population Council’s] submission dated September 15, 2000 . . . replace all previous commitments”³⁷³

- (1) “A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention.”³⁷⁴
- (2) “A surveillance study on outcomes of ongoing pregnancies.”³⁷⁵

FDA stated that “[p]revious study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.”³⁷⁶ The agency, thus, compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate Phase IV study.³⁷⁷ The Approval Letter explained that

³⁷³ Mifeprex Approval Letter, *infra* Appendix A, at 2.

³⁷⁴ Mifeprex Approval Letter, *infra* Appendix A, at 3. The Population Council acknowledged three weaknesses of this study. First, the sample size would be limited so that the sponsor “will only be able to determine whether the combined safety rates of hospitalizations, medically necessary surgical interventions, and IV fluids in each of the two cohorts are within plus or minus 5 percentage points of the expected 2% rate. We will not be able to detect differences of individual safety outcomes such as blood transfusions and deaths.” See Amendment 062 to the NDA, Revised Materials (Sept. 19, 2000): at 3. [FDA FOIA Release: MIF 007896-7903]. Second, the Population Council predicted that it might have difficulty finding women who were referred to another provider for care. *Id.* at 3-4. Third, it might be difficult to find women who did not return for their follow-up visit. *Id.* at 4. These three study weaknesses appear, at least in part, to stem from faulty selection criteria for study subjects. Patients should not be enrolled in a study unless they are willing to comply with follow-up visits and telephone inquiries. Additionally, informed consent forms authorize investigators to request medical records from other health care providers.

³⁷⁵ Mifeprex Approval Letter, *infra* Appendix A, at 3.

³⁷⁶ Mifeprex Approval Letter, *infra* Appendix A, at 3. These issues were characterized by the sponsor as “Secondary Study Objectives.” See Amendment 062 to the NDA (Sept. 19, 2000): at 1. The failure to consider each issue in a separate study is likely to compromise the quality of the data generated. Because the study is primarily focused on a provider-level variable (ability to provide surgical intervention), the study will not necessarily yield a meaningful sample size for each of the relevant patient-level variables (age and smoking status). Patients will be enrolled “consecutively from each provider until the provider’s quota is met.” See *id.* at 2.

³⁷⁷ The Population Council submitted data from the Spitz Study on 106 women age 35 and older and 51 patients under age 20. See Mifeprex Approval Letter, *infra* Appendix A, at 7. However, the effects and potential age-specific risks of the Mifeprex Regimen on women outside the tested age range deserve separate consideration in studies with far more subjects. Approximately 279,000 girls nineteen and younger and more than 84,000 women over the age of 35 obtain abortions in the United States annually. See Appendix B, *infra*, at B-4 (§§ 5 and 6). The Mifeprex Regimen, which directly interacts with the reproductive system, could conceivably interfere with pubertal development, as discussed above, and might pose unique risks to women who are nearing the end of their reproductive years.

“the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.”³⁷⁸

It appears, however, that the modifications came largely in response to the Population

5 Council’s unwillingness to explore the ramifications of the Mifeprex Regimen. On August 18, 1999, the Population Council acknowledged its Phase IV commitments, but stated that “[w]e plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.”³⁷⁹

The Population Council complained, for example, that “[a] prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome,

10 might result in an invasion of women’s privacy and would not likely produce a meaningful scientific result for decades.”³⁸⁰ Similarly, the Population Council informed FDA that it was “not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing

³⁷⁸ Mifeprex Approval Memo, *infra* Appendix A, at 7. FDA’s conclusion that the reduction to only two Phase IV studies “reflect[s] current postmarketing questions” ignores a number of issues about Mifeprex that remain unexplored. Because mifepristone interferes with pregnancy by binding to the progesterone receptor in the placenta, there is concern that the drug may affect not only the uterus, but the brain, breasts, adrenal glands, ovaries, and immune cells, all of which also have progesterone receptors. Concerns that mifepristone may have a carcinogenic effect on breast tissue have also been expressed. *See, e.g.*, Testimony of Dr. Joel Brind, FDA Hearings Transcript, *infra* Appendix A, at 172-175. Mifepristone also could affect the pituitary gland, the adrenal glands, and immune cells, all of which have glucocorticoid receptors. In addition, it is unclear whether a woman who undergoes multiple mifepristone-misoprostol abortions could suffer adverse effects. *See* ACOG Practice Bulletin, *infra* Appendix A, at 9 (“No well-designed prospective studies address the issue of repeat medical abortion.”). Questions also remain about possible effects on the children born to women who have terminated a previous pregnancy with the Mifeprex Regimen. *See, e.g.*, P. Van der Schoot and R. Baumgarten, “Effects of Treatment of Male and Female Rats in Infancy with Mifepristone on Reproductive Function in Adulthood,” *Journal of Reproduction and Fertility* 90 (1990): 255-66 (finding that rats exposed to mifepristone in their infancy suffered infertility in adulthood)[FDA FOIA Release: MIF 007165- 007176].

³⁷⁹ Medical Officer’s Review, *infra* Appendix A, at 24 (quoting from the Population Council’s submission to FDA on Aug. 18, 1999).

³⁸⁰ Medical Officer’s Review, *infra* Appendix A, at 24 (quoting from the Population Council’s submission to FDA on Aug. 18, 1999); *see also* Mifeprex Approval Memo at 7 (agreeing with the Population Council’s reasoning).

this, as it could violate women's privacy."³⁸¹ The Population Council's concerns about privacy lack merit. Patients who participate in clinical trials give their consent to participate and to be monitored, thus eliminating concerns about privacy. Similarly, FDA should not have accorded undue weight to the Population Council's protestations about the potential expense of the trials; drug sponsors, who stand to profit from a drug's sales, are responsible for bearing the expenses incurred in establishing the safety and efficacy of a drug.³⁸²

FDA's acquiescence in the Population Council's reduction in its Phase IV commitments compounded the Agency's earlier failure to require the sponsor to conduct clinical trials in accordance with the requirements of Section 314.126 of FDA's rules. FDA's inadequately justified curtailment of the sponsor's Phase IV study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

³⁸¹ Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999). The necessity of long-term monitoring is particularly critical to compensate for the unusually short tracking periods employed in the U.S. Clinical Trial, in which investigators generally did not track patients after their third visit. See Spitz Article, *infra* Appendix A, at 1242. "Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted." *Id.* Five percent of the participants in the U.S. Clinical Trial were not tracked through the third visit (which would have occurred on Day 15) because they failed to return for it, suggesting that each of these women was last seen on Day 3, only 2 days after the initial administration of mifepristone. See Medical Officer's Review, *infra* Appendix A, at 10. Abbreviated follow-up periods run counter to ICH standards, which state that in clinical trials of drugs intended for use during pregnancy, "followup of the pregnancy, fetus, and child is very important." *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.1.4.3) ("Special populations").

³⁸² In fact, the sponsors of Mifeprex received substantial outside funding to support their efforts. See "Mifepristone: FDA Approval Imminent, Advocates Predict," *Kaiser Daily Reproductive Health Report* (Sept. 28, 2000) (available at: <<http://www.kaisernetwork.org/reports/2000/09/kr000928.3.htm>>) ("Danco Laboratories, LLC, a small New York-based company, will market the drug with funding from billionaire financier Warren Buffet and hedge-fund czar George Soros and a \$10 million loan from the David and Lucile Packard Foundation."); Sharon Bernstein, "Persistence Brought Abortion Pill to U.S.," *Los Angeles Times* (Nov. 5, 2000): at A1 ("The Population Council raised \$16 million from like-minded foundations, including the Open Society Institute of New York, which is the philanthropic arm of billionaire George Soros, and the California-based Kaiser Family Foundation.").

IV. PETITIONERS SEEK LEAVE TO AMEND

The Petitioners respectfully inform FDA that they may file amendments to this Petition as information becomes available from Freedom of Information Act requests made before the
5 filing date of this document.³⁸³

V. CONCLUSION

10 For the foregoing reasons, the Petitioners respectfully request that the Commissioner immediately enter an administrative stay to halt any further distribution and marketing of Mifeprex until final agency action is taken on this Petition. The Petitioners also respectfully request that the Commissioner revoke approval of Mifeprex for the medical termination of
15 pregnancies less than 49 days' gestation. On the basis of the evidence presented above, the Petitioners respectfully request a full FDA audit of the French and U.S. Clinical Trials.³⁸⁴

³⁸³ The Petitioners have filed numerous Freedom of Information Act ("FOIA") requests with FDA that remain unanswered, including: 1) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of FDA's letter to the Population Council dated, or mailed, on or about June 1, 2000, along with any attachments, appendices, and other accompanying materials"); 2) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of the new drug application . . . filed . . . on or about March 18, 1996 (NDA 20-687)"); 3) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001) (seeking a copy of data submitted by the sponsor "related to the use of mifepristone by women over the age of thirty-five, females under the age of eighteen, and women who smoke" and of the Phase IV study protocols submitted by the Sponsor and any Phase IV trial data); and, 4) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Feb. 6, 2002) (seeking a correct listing of all drug applications approved pursuant to 21 C.F.R. § 314.520 and documents detailing FDA's reasoning for approving drugs under this section of its rules).

³⁸⁴ An audit of the U.S. Clinical Trial is additionally warranted because of an unusual data management decision made by the Population Council with the apparent approval of the FDA:

Thank you for speaking with me the other day about our data dilemma. In response to our conversation, we have decided to create two versions of our electronic database from the mifepristone study. The first will reflect exactly the physical copies of the patient record forms, and will be used as the basis for our regulatory submissions to you. The second version will closely match the first, particularly on safety and efficacy indicators, but certain variables will be modified to create an internally consistent database that we can use easily for our planned scholarly publications on the topic. We will keep careful track of the changes we make and we will be able to explain them to an FDA auditor should the need arise. One result

VI. ENVIRONMENTAL IMPACT

This Petition for withdrawal of approval of an NDA is categorically excluded under 21
5 C.F.R. § 25.31(d). An environmental impact statement is, thus, not required.

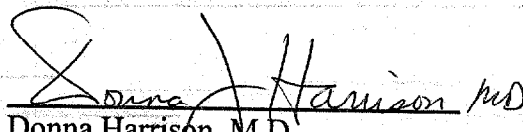
VII. ECONOMIC IMPACT

10 The Economic Impact information shall be submitted only when and if requested by the
Commissioner following review of the Petition, in accordance with 21 C.F.R. § 10.30.

CERTIFICATIONS AND SIGNATURES

15 On behalf of the petitioner organizations listed below, we the undersigned hereby certify
that, to the best of petitioners' knowledge, this Citizen Petition is true and accurate. It includes
all available information relevant to this Petition, including information both favorable and
unfavorable to Petitioners' position in this matter.

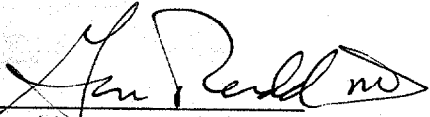
20 So executed this 15 day of August 2002.


Donna Harrison, M.D.
Chairperson, Subcommittee on Mifeprex
25 American Association of Pro-Life
Obstetricians and Gynecologists
P.O. Box 414
Eau Claire, MI 49111
30 Phone: (616) 921-2513

of this approach to handling the data is that certain aspects of our future publications may differ from
tabulations that appear in our regulatory submissions.

Letter, Charlotte Ellertson, Population Council, to [Redacted], FDA/CDER (July 28, 1997): at 1 [FDA FOIA Release:
MIF 006489].

So executed this 13 day of August 2002.


Gene Rudd, M.D.
Associate Executive Director
Christian Medical Association
P.O. Box 7500
Bristol, TN 37621
Phone: (423) 844-1000

5

So executed this 20th day of August 2002.

Sandy Rios
Sandy Rios, President
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1015 Fifteenth Street, N.W.
Suite 1100
Washington, D.C. 20005
Phone: (202) 488-7000

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Citizen Petition (Mifeprex) Documents

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Exhibit A: Selected Bibliography.	A
Exhibit B: Statistics Used in the Petition.	B
Exhibit C: FDA's Subpart H Webpage (Chart).	C
Exhibit D: Printouts from Mifeprex abortion websites illustrating deviations from the approved regimen.	D
David Willman, "How a New Policy Led to Seven Deadly Drugs," <i>Los Angeles Times</i> (Dec. 20, 2000): at A1.	E
Kit R. Roane, "Replacement Parts: How the FDA Allows Faulty, and Sometimes Dangerous, Medical Devices onto the Market," <i>U.S. News & World Report</i> (July 29, 2002): at 54-59.	E
F-D-C Reports, "RU-486 Action Date is Sept. 30," <i>The Pink Sheet</i> (June 12, 2000): 14.	F
Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," <i>Wall Street Journal</i> (Oct. 18, 2000): B1.	G
Dennis F. Thompson, "Surrogate End Points, Skepticism, and the CAST Study," <i>Annals of Pharmacotherapy</i> , 36 (January 2002): 170-71.	H
Mitchell D. Creinin, "Early Medical Abortion with Mifepristone or Methotrexate: Overview," in <i>Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations 3</i> (Washington, D.C.: 2000): 1-32; "National Abortion Federation (NAF) Protocol for Mifepristone and Misoprostol in Early Abortion" in <i>Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations</i> (Washington, D.C., 2000): 33-37; "National Abortion Federation (NAF) Protocol for Methotrexate and Misoprostol in Early Abortion" in <i>Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations</i> (Washington, D.C., 2000): 38-45.	I
Ralph W. Hale, M.D., and Stanley Zinberg, M.D., "The Use of Misoprostol in Pregnancy," <i>New England Journal of Medicine</i> 344 (Jan. 4, 2001): 59-60.	J
Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," <i>Univ. of Virginia Law Review</i> 82: (1996): 1753-1866 (selected pages).	K
Mitchell D. Creinin and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," <i>American Journal of Obstetrics and Gynecology</i> 180 (1999): 35-41.	L
Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," <i>New York Times</i> (June 8, 2000): A21	M
Beth Kruse, et al., "Management of Side Effects and Complications in Medical Abortion," <i>American Journal of Obstetrics and Gynecology</i> 183 (2000): S65-75.	N
American College of Obstetricians and Gynecologists, "Medical Management of Abortion." <i>ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician Gynecologists</i> 26 (April 2001)("ACOG Practice Bulletin").	O

Citizen Petition (Mifeprex) Documents

2

Description of Article/Document	TAB
Elizabeth Aubény, et al., "Termination of Early Pregnancy (Up to After 63 Days of Amenorrhea) With Mifepristone (RU 486) and Increasing Doses of Misoprostol," <i>International Journal of Fertility</i> 40 (1995): 85-91.	P
Carol Jouzaitis, "Doctor's Abortion-drug Technique Draws Fire," <i>Chicago Tribune</i> (Sept. 12, 1994): sec. 1, p. 1 & 14.	Q
Denise Gellene, "RU-486 Abortion Pill Hasn't Caught on in U.S.," <i>Los Angeles Times</i> (May 31, 2001): A1.	R
Susan Okie, "Physicians Sent Abortion Pill Alert," <i>Washington Post</i> (Apr. 18, 2002): A2.	S
Claudette Hajaj Gonzalez, et al., "Congenital Abnormalities in Brazilian Children Associated with Misoprostol Misuse in First Trimester of Pregnancy," <i>The Lancet</i> 351 (1998): 1624-27.	T
Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," <i>American Journal of Obstetrics and Gynecology</i> 168 (1993): 903-908.	U
Ivar K. Rossavik, George O. Torjusen, and William E. Gibbons, "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in <i>in Vitro</i> Fertilization Pregnancies," <i>Fertility and Sterility</i> 49 (1988): at 1012-17.	U
êda M. Orioli and Eduardo E. Castilla, "Epidemiological Assessment of Misoprostol Tetratogenicity," <i>British Journal of Obstetrics and Gynaecology</i> 107 (April 2000): 519-23.	V
F.R. Vargas, et al., "Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case Control Study," <i>American Journal of Medical Genetics</i> 95 (2000): 302-306.	W
Marc Kaufman and Ceci Connolly, "U.S. Backs Pediatric Tests In Reversal on Drug Safety," <i>Washington Post</i> (April 20, 2002): A3.	X
William J. Eaton, "Path Cleared for Abortion Pill Use Medicine: French Maker of RU-486 Gives Patent Rights to a Nonprofit Group," <i>Los Angeles Times</i> (May 17, 1994): A1.	Y
Sharon Bernstein, "Persistence Brought Abortion Pill to U.S.," <i>Los Angeles Times</i> (Nov. 5, 2000): at A1.	Z

EXHIBIT 16

FDA Letter to Population Council re NDA (Feb. 18, 2000)

/S/

NDA 20-687

FEB 18 2000

Population Council
Attention: Sandra P.-Arnold
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mifepristone 200 mg tablets.

We acknowledge receipt of your submissions dated September 18 and 26, 1996; January 30, March 6 and 31, July 28, August 5, September 3 and 24, November 26, 1997; January 30, February 19, April 27, June 25, October 26, December 7 and 8, 1998; February 8, 22, March 31, April 28, May 10, 20, June 3 (2), 15, 25, 30, July 14, 22, August 3, 13, 18, 30, September 3, 8, 13, 30, October 5, 26, 28, November 16, 29 (2), December 6, 7, 23, 1999; January 21, 28 (2), and February 16, 2000. Your submission of August 18, 1999 constituted a complete response to our September 18, 1996 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry

Drug Substance

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Mifepristone
Population Council
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Drug Product

Redacted 1
pages of trade
secret and/or
confidential
commercial
information

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Mifepristone
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Labeling

Address the recommendations in the enclosed draft labeling for the Physician Insert and Patient Package Insert.

It will be necessary for you to submit revised draft labeling for the drug. We recommend that the

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Mifepristone
Population Council
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labeling be identical in content to the enclosed draft labeling (text for the Physician Package Insert and Patient Package ~~Insert~~).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system,
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of the method failure,
3. To assess the long-term effects of multiple use of the regimen,
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not,
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke,
6. To ascertain the effect of the regimen on children born after treatment failure.

Distribution Plan

We have completed our review of this application, including the restrictions on the distribution and use of this product proposed in your January 21, 2000 submission, entitled "Distribution Plan". We have concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended. The restrictions on distribution will need to be amended.

We have thus considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and have concluded that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product.

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Promotional Activities

Please note that promotional activities for this NDA are subject to 21 CFR 314.550. As such, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the [redacted] and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call [REDACTED]

Sincerely,

/S/

Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 17

FDA Approval Letter for Mifeprex (Sept. 28, 2000)

SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

App. 000417

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

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2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call

Sincerely,

/s/

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 18

FDA Approval Memo to Population Council re NDA 20-687 Mifeprex (Sept. 28, 2000)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2000

FROM:

/S/

SUBJECT:

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and 1.3% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregnancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

"If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains [REDACTED] Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from [REDACTED] in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenómelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided [REDACTED] 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H. (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
 - Ability to assess the duration of pregnancy accurately
 - Ability to diagnose ectopic pregnancies
 - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
 - Has read and understood the prescribing information of Mifeprex
 - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
 - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
 - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
 - Must record the Mifeprex package serial number in each patient's record
- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
 - Secure manufacturing, receiving, and holding areas for the drug
 - Secure shipping procedures, including tamper-proof seals
 - Controlled returns procedures
 - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
 - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
 - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Spitz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 19

2003 Citizen Petitioners' Response to Opposition Comments filed by The Population Council, Inc. and Danco Labs, LLC

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**Re: Docket No. 02P-0377
Response to Opposition Comments filed by The Population Council, Inc. and
Danco Laboratories, LLC**

We submit these comments on behalf of The American Association of Pro Life Obstetricians and Gynecologists (“AAPLOG”), the Christian Medical Association (“CMA”), and Concerned Women for America (“CWA”) (collectively, “the Petitioners”), in response to Opposition Comments filed by the makers/distributors of Mifeprex™ (mifepristone) 200 mg tablets (NDA 20-687).¹ In particular, The Population Council, Inc. (“the Council”) and Danco Laboratories, LLC (“Danco”) (collectively, “the Sponsor”) submitted comments on March 13, 2003 opposing the Citizen Petition and Request for Administrative Stay (“Petition”) filed by the Petitioners on August 20, 2002.²

Not surprisingly, the Council and Danco ask the Food and Drug Administration (“FDA”) to maintain the status quo, so that they can continue to sell Mifeprex, a “non-surgical” alternative to abortion. By contrast, the Petitioners seek to protect women from the unknowing use of a dangerously unsafe drug by pursuing an immediate stay and withdrawal of FDA’s approval of the new drug application (“NDA”) for mifepristone.

Although opposing comments were inevitable, the Petitioners are concerned that the Sponsor has refused to acknowledge any problems regarding the safety, effectiveness and overall

¹ Opposition of The Population Council, Inc. and Danco Laboratories, LLC to Citizen Petition and Request for Administrative Stay Regarding Mifeprex® (Mifepristone), Docket No. 02P-0377 (March 13, 2003) (“Opposition Comments”) (available at: <<http://www.fda.gov/ohrms/dockets/dailys/03/Mar03/031303/031303.htm>>).

² Citizen Petition of the American Association of Pro Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America, Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days’ Gestation, Docket No. 02P-0377 (filed Aug. 20, 2002) (available at: <<http://www.aaplog.org/newscitizenpetitionru486.htm>>).

medical suitability of the Mifeprex Regimen.³ The Petitioners are not surprised, however, that the Sponsor has failed to produce medical-scientific data and adequate explanations for the administrative irregularities described in the Petition. This failure is consistent with the Petitioners' contention that the clinical data in support of the Mifeprex Regimen are scarce, not the product of adequate and well-controlled trials, and cannot support a reasoned risk-benefit analysis by FDA. Instead, the available evidence points to the fact that Mifeprex should never have been approved by FDA.

We have set forth below our responses to the Sponsor's Opposition Comments, along with additional evidence that the safety and effectiveness of Mifeprex have not been established in accordance with FDA's regulations. In particular, the drug, which was not lawfully entitled to consideration under Subpart H, could not have been approved apart from that provision's special distribution restrictions; the clinical trials relied on to support the NDA were legally and clinically insufficient; the inclusion of misoprostol in the Mifeprex Regimen without a corresponding misoprostol approval was unlawful; and the Regimen's use is inherently unsafe, as proven by recent life-threatening adverse events and even deaths. With this evidence, FDA is both statutorily empowered and obligated to grant an Administrative Stay to suspend the Mifeprex NDA approval and expedite withdrawal proceedings.

I. The Safety and Effectiveness of Mifeprex Have Not Been Established in Accordance with FDA's Regulations.

FDA's approval of a drug product must rest on the Agency's conclusion that the drug is safe and effective for its labeled conditions for use. In the case of Mifeprex, the Petitioners previously provided evidence that the NDA should not have been approved, and the Sponsor's Opposition Comments did not rebut that evidence. In fact, as described below, although the Opposition Comments reiterate the Sponsor's confidence in the safety and efficacy of the Mifeprex Regimen, they also expose the dearth of pre- or post-approval evidence for that position. Consequently, given the body of evidence now before FDA, the Agency should withdraw its approval of the Mifeprex NDA at this time.

A. Subpart H Enables FDA to Place Special Restrictions on Especially Risky Drugs like Mifeprex.

Although Petitioners maintain their original position that FDA's reliance on Subpart H was unlawful for this drug, the Sponsor's response that Mifeprex could have been approved alternatively under Section 505 is incorrect. The Sponsor's Opposition Comments repeat an argument that the Sponsor made when it was trying to convince FDA not to use Subpart H – that “[t]he restrictions FDA imposed under Subpart H could as well have been imposed (and enforced) under Section 505 [of the FD&C Act]⁴ itself, without reference to Subpart H.”⁵ The

³ When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Response, “Mifeprex Regimen” will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

⁴ Federal Food, Drug, & Cosmetic Act of 1938 (“FD&C Act”), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

fact that FDA proceeded under Subpart H suggests that the Agency did not subscribe to this argument. Indeed, had FDA taken this position, it would not have promulgated the restricted distribution prong of Subpart H,⁶ but would simply have relied on Section 505 to impose restrictions. When FDA adopted Subpart H, it noted that “the restrictions to ensure safe use contemplated for approvals under [Subpart H] are authorized by statute.”⁷ FDA went on to explain that Subpart H would enable the Agency to impose on drugs restrictions “necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use.”⁸ Additional restrictions are necessary because Mifeprex and other Subpart H drugs carry greater risks than drugs approved through the typical new drug approval processes.⁹ In short, when FDA adopted Subpart H, it added a new tool to its regulatory toolbox enabling it to approve drugs that otherwise could not have been approved because the safe usage mandates in Section 505 would not have been satisfied.¹⁰ Therefore, the Sponsor errs in asserting that the approval of the Mifeprex NDA is independently grounded in Section 505(d).

The Sponsor also claimed that its cooperation with FDA to devise restrictions obviates the need to rely on Subpart H.¹¹ The Sponsor’s unfailing confidence in the safety of mifepristone even in the face of scientific evidence to the contrary is part of the reason that restrictions under section 505 could not be effective. The Sponsor’s bias in favor of Mifeprex clouds its analysis of the inherent hazards of the Regimen. In fact, the Sponsor refused to participate in devising restrictions that were designed to protect Mifeprex patients.

As “evidence” of its cooperation, the Sponsor pointed to the restricted distribution plan it proposed to an FDA advisory committee in 1996.¹² The FDA Advisory Committee’s reaction to

⁵ See Opposition Comments at 3 (citing 21 U.S.C. § 355). See also Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 3-5 [FDA FOIA Release: MIF 001333-49].

⁶ 21 C.F.R. § 314.520.

⁷ New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942, 58951, § 20 (Dec. 11, 1992) (“*Subpart H Final Rule*”).

⁸ *Subpart H Final Rule*, 57 Fed. Reg. at 58951, § 20. See also New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234, 13237, sec. III.B.3. (April 15, 1992) (“*Subpart H Proposed Rule*”) (noting that without Subpart H restrictions, the drug “would be adulterated under section 501 of the act, misbranded under section 502 of the act, or not shown to be safe under section 505 of the act”).

⁹ See *Subpart H Final Rule*, 57 Fed. Reg. at 58952, § 23 (“The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction.”).

¹⁰ FDA explained that “rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing.” *Subpart H Final Rule*, 57 Fed. Reg. at 58951-52, § 20.

¹¹ See Opposition Comments at 5-6.

¹² See Opposition Comments at 4. The Sponsor was referring to a plan presented to FDA’s Reproductive Health Drugs Advisory Committee (“FDA Advisory Committee”). See FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 7 (July 19, 1996) (*FDA Hearings Transcript*) [FDA FOIA Release: MIF 005200-90, MIF 005209]. The Petitioners will, at times, cite to documents

the proposal, however, reveals its inadequacy; the Advisory Committee stated that “[w]e agree in concept with the proposal but have serious reservations on how it is currently described in terms of assuring safe and adequate credentialing of providers.”¹³ The Sponsor also cited to its “comprehensive distribution plan” submitted in January 2000 and to its revised distribution plan submitted to FDA in March 2000.¹⁴ The Sponsor indicated in its January 2000 submission that it was providing the proposal only “in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns,”¹⁵ and the March 2000 submission was prefaced with a denial that mifepristone was “a highly toxic and risky drug.”¹⁶ However, as the Petition explained, the plans that the Sponsor submitted on both occasions were not designed with the safety of the patient in mind and when FDA proposed a set of restrictions that focused on patient safety, the Sponsor balked.¹⁷ Further, even if the Sponsor had participated willingly in drawing up restrictions that embodied key safeguards for patients, FDA could not necessarily expect similar cooperation from future generic producers of mifepristone.¹⁸

Conclusion

As explained above, the Mifeprex approval cannot rest independently on Section 505(d) of the FD&C Act. The Sponsor refused to acknowledge that there are serious risks associated with the Mifeprex Regimen, let alone to propose restrictions designed to counteract those risks. FDA approved Mifeprex under Subpart H in order to impose mandatory safety restrictions on the distribution and use of the drug. That being said, the proper course would have been for FDA to have rejected the NDA because Mifeprex is unsafe and ineffective under Section 505 and fails to satisfy the Subpart H prerequisites that it treat a serious or life-threatening illness and provide a meaningful therapeutic benefit above existing treatments.¹⁹

contained in FDA’s January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act (“FOIA”) request (“FDA FOIA Release”) filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page of the document cited, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <<http://www.fda.gov/cder/archives/mifepristone/default.htm>>.

¹³ FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45, MIF 000545] (citing statement voted on unanimously by the FDA Advisory Committee).

¹⁴ See Opposition Comments at 4-5.

¹⁵ Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26, MIF 000525]. The Sponsor’s reference to the “unique situation surrounding abortion provision in the United States” reveals the Sponsor’s primary concern in proposing restrictions, namely that the safety and confidentiality of *abortion providers* be maintained, not that patient safety be maximized.

¹⁶ Responses by Population Council to “FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)” (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24, MIF 000523].

¹⁷ See Section I.D. herein; see also Petition at 50-54.

¹⁸ See FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85, MIF 000585] (“Subpart H approval will also allow the FDA to impose similar distribution restrictions and system on any future generic mifepristone approved for this indication.”).

¹⁹ See Petition at 18-23 (explaining why Mifeprex was an inappropriate candidate for Subpart H).

B. The Mifeprex Clinical Trials Were Legally and Clinically Insufficient.

The Petition describes numerous problems that plagued the clinical trials underlying the approval of Mifeprex. The Sponsor's Opposition Comments, rather than demonstrating the sufficiency of the clinical trial data that formed the basis for the Mifeprex NDA, heightened the Petitioners' concerns about the legal and clinical sufficiency of the French and U.S. Clinical Trials (collectively, "Mifeprex Trials"). First, a close reading of the Sponsor's Opposition Comments reveals that the Mifeprex Trials were not historically controlled but, rather, were *uncontrolled*.²⁰ Second, even if the Mifeprex trials were historically controlled, as the Sponsor maintains, the use of historically controlled trials to support this NDA violated clearly established FDA rules and agency policies.²¹ Finally, the Sponsor's additional arguments in support of the scientific adequacy of the Mifeprex trials do not answer the objections presented in the Petition. Untested by adequate clinical trials, the Mifeprex Regimen cannot be deemed to be safe and effective; accordingly, the marketing of Mifeprex must be halted.

1. The Mifeprex Trials Were Uncontrolled.

A review of the record regarding the scope and methodology of the trials, prompted by the Sponsor's defense of the Mifeprex Trials,²² reveals that the trials used to support the Mifeprex NDA were not historically controlled, but were *uncontrolled*.²³ The Petition cited to the discussion between a member of FDA's Advisory Committee and an FDA official in which the Mifeprex Trials were characterized as "historically" controlled.²⁴ The Petitioners noted, however, that the Mifeprex Trials appeared to have been uncontrolled.²⁵

The French Clinical Trials consisted of two studies in which all participants were given a mifepristone-misoprostol regimen, and no concurrent control group underwent a different abortion treatment.²⁶ The Sponsor did not describe any historical (or "external") control group,²⁷

²⁰ Because the Mifeprex Regimen was the first drug regimen that FDA approved to induce abortions, in order to scientifically demonstrate the safety and effectiveness of this drug regimen, the Sponsor should have compared this new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period.

²¹ The Petitioners believe that a longitudinal analysis of all past occasions on which FDA accepted uncontrolled and historically controlled trials as an adequate basis for an NDA and all past occasions on which it has rejected the use of uncontrolled or historically controlled clinical trials would demonstrate the inadequacy of the clinical trials underlying this NDA. FDA is uniquely qualified to perform such an analysis.

²² See Opposition Comments at 6-9.

²³ One consequence of the failure to conduct properly controlled trials is that a *statistical* evaluation of effectiveness could not be made. As FDA's statistical reviewer noted, with reference to the French trials: "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy." See FDA, Statistical Review and Evaluation (May 21, 1996): at 7-8.

²⁴ Petition at 36, n.168 (referring to statements by Dr. Cassandra Henderson, a member of the FDA Advisory Committee, and FDA's Dr. Ridgely C. Bennett at the Advisory Committee Hearings).

²⁵ Petition at 35.

²⁶ Letter, C. Wayne Bardin, Population Council, to FDA/CDER (June 5, 1995) (Submission Serial Number: 131) at 3-4 ("Bardin Letter") [FDA FOIA Release: MIF 004746-47]. The patients in the French Clinical Trials took 600 mg of mifepristone followed by 400 µg of misoprostol. In one of the French Clinical Trials, some patients received an

nor did the Sponsor indicate that any of the well-established scientific guidelines for selecting a proper control group before commencing a historically controlled study were used for the French Clinical Trials.²⁸ The Sponsor, nevertheless, informed FDA that “[a]ll studies conducted with mifepristone in the induction of abortion can be regarded as having historical controls which consist of the body of information available on abortion using surgical procedures.”²⁹ This observation appears to be the only basis for the Sponsor’s claim that the French Clinical Trials were historically controlled, and it is inadequate.

The U.S. Clinical Trial mimicked the design of the French Clinical Trials.³⁰ All participants were given a mifepristone-misoprostol regimen, and no concurrent control group underwent a different abortion treatment. Descriptions of the U.S. Clinical Trial do not mention a control group, historical or otherwise, or the procedures according to which a control group was selected.³¹ The absence of any reference to a control group suggests that the U.S. Clinical Trial was not historically (externally) controlled.³²

The Sponsor’s failure to precisely identify a historical control group is fatal to its claim that the Mifeprex Trials were historically controlled. Postulating the existence of some generic,

extra 200 µg of misoprostol if the first 400 µg was not sufficient to complete the abortion. The approved Mifeprex Regimen consists of 600 mg of mifepristone followed by 400 µg of misoprostol.

²⁷ Bardin Letter at 3-4.

²⁸ FDA guidance lists “some approaches to design and conduct of externally controlled trials could lead them to be more persuasive and potentially less biased:”

A control group should be chosen for which there is detailed information, including, where pertinent, individual patient data regarding demographics, baseline status, concomitant therapy, and course on study. The control patients should be as similar as possible to the population expected to receive the test drug in the study and should have been treated in a similar setting and in a similar manner, except with respect to the study therapy. Study observations should use timing and methodology similar to those used in the control patients. To reduce selection bias, selection of the control group should be made before performing comparative analyses; this may not always be feasible, as outcomes from these control groups may have been published. Any matching on selection criteria or adjustments made to account for population differences should be specified prior to selection of the control and performance of the study.”

FDA, “Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials,” (Rockville, Md.: May 2001): at 27 (§ 2.5.2) (*ICH: E10*). *ICH: E10* is available at: <<http://www.fda.gov/cder/guidance/4155fnl.pdf>>.

²⁹ Bardin Letter at 4.

³⁰ For a description of the U.S. Clinical Trial, see Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri Benton, M.D., and Ann Robbins, “Early Pregnancy Termination with Mifepristone and Misoprostol in the United States,” *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 (“Spitz Article”) [FDA FOIA Release: MIF 006692-97].

³¹ See, e.g., Spitz Article.

³² The Spitz Article does compare two groups, patients who are differentiated by the age of their pregnancies, but a comparison of that type does not generate data about whether mifepristone-misoprostol abortions are safe and effective. To the extent the Sponsor believed that a correlation existed between the age of the pregnancy and the safety and efficacy of mifepristone-misoprostol abortions, any historical control group that the Sponsor used should have been classified by, among other characteristics, gestational age.

undefined comparison group based on the literature about surgical abortion does not suffice.³³ In sum, the Mifeprex Trials were uncontrolled and cannot support the Mifeprex NDA.³⁴

2. Mifeprex Is Not a Drug for Which Historically Controlled Trials Were Appropriate.

Assuming arguendo, as the Sponsor maintains, that the Mifeprex Trials were historically controlled, they were nevertheless not *adequately* controlled and did not provide an adequate basis for approving the Mifeprex NDA. In its Opposition Comments, the Sponsor erroneously suggested that “historically controlled” trials yield data of the same quality as data generated in concurrently controlled trials.³⁵ In fact, the scientific community (and FDA specifically) regard historically controlled studies to be little better than uncontrolled studies and, therefore, generally disfavor their use with a few well-defined exceptions.³⁶

Mifepristone-misoprostol abortions do not fall within any of those exceptions. The Rochester Glossary states that historical controls are “mainly used in the study of rare diseases” in which sample size would not be sufficient to support a randomized clinical trial.³⁷ This exception is inapplicable because the number of pregnant women seeking to terminate their pregnancies is large enough to support randomized, concurrently controlled trials. Section 314.126(b)(2)(v) of FDA’s rules cautions that the use of historical controls is “usually reserved

³³ In addition, the Sponsor, in its Opposition Comments, invented a historical control group *ex post facto* by comparing the rate of spontaneous abortions in the general population of pregnant women with the rate of abortions in patients who underwent a mifepristone-misoprostol regimen during the Mifeprex Trials. See Opposition Comments at 6-7 (“In these major studies, 92-95% of the 2508 women evaluated for efficacy had complete abortions By comparison, the rate of spontaneous abortion in the first trimester is assumed to be about 10%.”). Using the general population as a historical control group and retrospectively assuming a rate of spontaneous abortion in this group is not a scientifically acceptable approach to identifying a control group, particularly when, as here, an established surgical treatment group could have been used as the control group.

³⁴ Section 314.126(e) of FDA’s rules states that “[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness.” 21 C.F.R. § 314.126. A publicly available FDA staff presentation about clinical trials illustrates this point. The presentation explained, under the heading “Phase 3 – Comparative trial to evaluate drug,” “Comparator group important – Standard of care, placebo, never nothing in serious or life-threatening diseases (ICH E3, E9, E10).” See Peter A. Lachenbruch, “Some Things You Always Wanted to Know about Clinical Trials but Were Afraid to Ask,” Slide Presentation for *CBER 101: An Introduction to the Center for Biologics Evaluation and Research (CBER)* (March 24-26, 2003): at 5 (emphasis in original) (available at: <http://www.fda.gov/cber/summaries/cber101032403pl.pdf>).

³⁵ See Opposition Comments at 6-8.

³⁶ For example, the Research Subjects Review Board of the University of Rochester Medical Center authored a guidance document, which states that “[h]istorical controls are considered to be the least reliable because they compare results obtained in another time, in another place and by another investigator.” University of Rochester Medical Center, Research Subjects Review Board, “Glossary of Research Terms,” at 2 (“Rochester Glossary”) (available at: <http://www.urmc.rochester.edu/rsrb/pdf/glossary.pdf>). Similarly FDA has explained, “[t]he limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, etc.) and deserve particular attention.” FDA/CDER, *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988): at 54.

³⁷ Rochester Glossary at 2 (“Historical controls are mainly used in the study of rare diseases where the **n** is not sufficient for a randomized clinical trial.”).

for special circumstances” and cites “studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).”³⁸ Mifepristone-misoprostol abortions do not fit within either of these categories. First, the Regimen does not treat a condition with “high and predictable mortality.” Second, the effects of the Regimen are not “self-evident” as in the case of general anesthetics. The Sponsor’s discussion of the adequacy of its trial data reflects the Sponsor’s fundamental misconception that there are only two possible outcomes of the Mifeprex Regimen, both of which are self-evident: regimen failure (failed abortion) and regimen success (death and complete expulsion of the fetus). The Sponsor’s focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes. Such outcomes include tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects.

The Sponsor’s reliance on FDA Guidance, *ICH: E10*, is also misplaced.³⁹ Although *ICH: E10* includes a discussion of situations in which externally controlled trials may be used, it also warns of their inherently problematic nature.⁴⁰ The Sponsor’s reliance on the acknowledgement in *ICH: E10* that historical controls are appropriate in some circumstances is misplaced. *ICH: E10* explains:

An externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course. It is often possible, even in these cases, to use alternative, randomized, concurrently controlled designs (see section 2.1.5).⁴¹

³⁸ 21 C.F.R. § 314.126(b)(2)(v) provides:

Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

³⁹ Opposition Comments at 7.

⁴⁰ See *ICH: E10* at 29 (§ 2.5.7) (“The externally controlled study cannot be blinded and is subject to patient, observer, and analyst bias; these are major disadvantages. It is possible to mitigate these problems to a degree, but even the steps suggested in section 2.5.2 cannot resolve such problems fully, as treatment assignment is not randomized and comparability of control and treatment groups at the start of treatment, and comparability of treatment of patients during the trial, cannot be ensured or well assessed. It is well documented that externally controlled trials tend to overestimate efficacy of test therapies. It should be recognized that tests of statistical significance carried out in such studies are less reliable than in randomized trials.”). See also Henry Sacks, Ph.D., M.D., Thomas C. Chalmers, M.D., Harry Smith, Jr., Ph.D., “Randomized Versus Historical Controls for Clinical Trials,” *The American Journal of Medicine* 72 (Feb. 1982): 233-240, 233 (“The data suggest that biases in patient selection may irretrievably weight the outcome of [historical controls] in favor of new therapies.”).

⁴¹ *ICH: E10* at 28 (§ 2.5.4).

Even proponents of mifepristone-misoprostol abortions would not argue that such abortions are superior to alternative methods of abortion.⁴² In fact, the Mifeprex Regimen has been shown to be an inferior method of abortion.⁴³ Absent a clear belief in the Regimen's superiority, concurrently controlled trials should have been performed.⁴⁴ Furthermore, pregnancies often do not follow a "well-documented, highly predictable course."⁴⁵ Mifepristone-misoprostol abortions do not satisfy either prong of the *ICH: E10* prerequisite for the use of historically controlled studies.⁴⁶

3. The Mifeprex Clinical Trials Did Not Establish a "Meaningful and Therapeutic Benefit" As Required By Subpart H.

Drugs, like Mifeprex, approved pursuant to Section 314.520 (Subpart H) of the Agency's rules,⁴⁷ must provide a "meaningful therapeutic benefit to patients over existing treatments."⁴⁸ Subpart H drugs "will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."⁴⁹ The Sponsor argued that "meaningful therapeutic benefit" does not impose design features for the clinical trials required to support an NDA approved pursuant to Subpart H.⁵⁰ The Sponsor's position is inconsistent with the plain meaning of the rule. Subpart H is reserved for drugs that have a higher risk profile than drugs approved through standard FDA processes. A meaningful therapeutic benefit over available therapies justifies the heightened risks, and only well-controlled clinical trials can demonstrate that such a benefit exists.⁵¹

⁴² See, e.g., Richard Hausknecht, M.D., "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003): 463-65, 465 ("Hausknecht Article") ("Which approach to early abortion, medical or surgical, is safer remains unknown but it does appear that medical abortion is as safe as early surgical abortion. There are no recent data on failed surgical abortions but the failure rate of mifepristone/misoprostol medical abortions is higher than that reported decades ago for suction curettage.")

⁴³ Petition at 21-22 (discussing Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study," *Contraception* 59 (1999): 153-159 [FDA FOIA Release: MIF 000438-44]).

⁴⁴ The Petitioners believe that trials comparing mifepristone-misoprostol abortion with the surgical alternative were not conducted for precisely this reason (*i.e.*, such trials would have demonstrated that mifepristone-misoprostol abortions were inferior). Because of its inferiority, the Mifeprex Regimen is contraindicated.

⁴⁵ Even though pregnancy occurs regularly, complications arise during pregnancy on a frequent basis (*e.g.*, approximately 2% of pregnancies are ectopic and others involve such complications as high blood pressure, ruptured placenta, infection, cysts, abnormal pain, anemia, and fetal malposition).

⁴⁶ Even if mifepristone-misoprostol abortion were deemed to be an acceptable candidate for historically-controlled testing, the Sponsor should have attempted to devise concurrently controlled trials anyway. *ICH: E10* states that even when historically controlled testing may be appropriate, "[i]t is often possible ... to use alternative, randomized, concurrently controlled designs." *ICH: E10* at 28 (§ 2.5.4).

⁴⁷ 21 C.F.R. § 314.520.

⁴⁸ 21 C.F.R. § 314.500.

⁴⁹ See *Subpart H Final Rule*, 57 Fed. Reg. at 58953, § 25.

⁵⁰ Opposition Comments at 8.

⁵¹ The Sponsor also argued that by the time FDA decided to approve Mifeprex using Subpart H, the Sponsor had completed the Mifeprex Trials and that FDA could not have required the Sponsor to modify the trial design and perform new trials for Subpart H purposes. See Opposition Comments at 9, n. 4. FDA is under no obligation to

The Sponsor argued that two of the examples of “meaningful therapeutic benefit” listed in Section 314.500 (“ability to treat patients unresponsive to, or intolerant of, available therapy”) present situations in which comparative trials with the existing therapy are not feasible.⁵² Yet, sponsors who intend their drugs to treat unresponsive or intolerant patients are not exempt from the requirement to conduct “well-controlled” trials. In fact, Subpart H trials are routinely designed to compare, in unresponsive or intolerant patients, the safety and effectiveness of the new therapy with either the standard of care or a placebo.⁵³

The Sponsor further claimed that FDA “routinely approves Subpart H drugs on the basis of study designs that do not compare the Subpart H drug directly to existing therapy.”⁵⁴ In support of this claim, the Sponsor offered one example, the Subpart H approval of the leprosy drug, Thalomid (thalidomide).⁵⁵ That example is inapposite because the Thalomid NDA was supported by three controlled trials despite the existence of factors that might have supported an exemption from the standard trial requirements.⁵⁶ In one of the three underlying trials, thalidomide plus the standard treatment was compared against the standard treatment alone plus a placebo.⁵⁷ This study design allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care – in direct contrast to the faulty study designs and minimal statistical analysis associated with the Mifeprex NDA.

Conclusion

By statute and agency regulation, drug applications must be supported by adequate and well-controlled studies. The failure of the Sponsor to offer legally and scientifically sufficient trial data should have been fatal to its NDA and now requires withdrawal of that approval.⁵⁸

approve an NDA at all, let alone to approve an NDA based on insufficient trial data. It is not uncommon at any stage of the NDA review process for FDA to require a drug sponsor to correct or amend an NDA by conducting properly designed and executed studies. Had the sponsor followed standard scientific norms and performed randomized, concurrently controlled trials comparing mifepristone-misoprostol abortion with surgical abortion it would have been able to supply comparative data.

⁵² See Opposition Comments at 8-9. Mifepristone-misoprostol abortions do not fall within either of these examples. Because surgical abortion, the standard of care, is the backup procedure if the Mifeprex Regimen fails, *ipso facto* the Regimen cannot be used to treat patients unresponsive to or intolerant of the standard of care.

⁵³ Furthermore, in this instance, the Sponsor did not attempt to test the drug in populations that it identified as intolerant or unresponsive and, indeed, the Mifeprex Regimen is not an option for patients unresponsive to or intolerant of surgical abortion because surgical abortion is the back-up procedure for Mifeprex patients.

⁵⁴ Opposition Comments at 9.

⁵⁵ NDA 20-785.

⁵⁶ The fact that leprosy is a rare disease in the U.S. makes it difficult to perform clinical trials. In addition, there are compassionate reasons for not awaiting the results of randomized, double-blinded comparator controlled clinical trials before treating patients suffering from leprosy. The fact that well-controlled trials were employed despite the existence of these mitigating factors is evidence of the value that the scientific community places on well-controlled trials.

⁵⁷ See Petition at 39 (discussing the thalidomide trials). In one study, all participants received either thalidomide or a placebo in addition to the standard dapsone treatment.

⁵⁸ See Petition at 30-35 (discussing statutory and regulatory requirements for clinical trials).

C. The Inclusion of Misoprostol in the Mifeprex Regimen Was Unlawful.

The Mifeprex Regimen combines the use of mifepristone and a second drug, misoprostol (CytotecTM). Although FDA never approved misoprostol as a stand-alone abortifacient, it approved misoprostol for use as an abortifacient in combination with mifepristone and mandated this use in the Mifeprex Package Insert. As explained in the Petition, FDA effectively sanctioned the use and promotion of misoprostol for an unapproved indication.⁵⁹ The promotion of an unapproved use contradicts the FD&C Act, which takes the position that “a drug manufacturer may not promote [its] product for any use other than the ones for which the company received FDA approval.”⁶⁰

In its Comment, the Sponsor defended the *de facto* approval of misoprostol for a new indication as an abortifacient and asserted that “FDA routinely approves drugs for use in combination with previously approved drugs without requiring any change in the labeling of the previously approved drug.”⁶¹ The Sponsor denied that this practice “puts either FDA or the sponsor of the later-approved drug in the position of ‘promoting’ off-label use of the previously approved drug.”⁶² The Sponsor offered four examples to support its position that this practice is not uncommon.⁶³

In fact, the Sponsor’s four examples support the position set forth in the Petition that subsequently approved drugs (Drug Bs – like Mifeprex) may reference previously approved drugs (Drug As – like misoprostol) on Drug B’s labeling only for *FDA-approved* indications.⁶⁴

⁵⁹ See Petition at 41-48. The drug’s manufacturer, G.D. Searle & Co. (“Searle”), did not file a supplemental NDA to obtain approval for misoprostol’s use as an abortifacient. Searle has subsequently been purchased, most recently, by Pfizer. See Petition at 42, n.188.

⁶⁰ See Elizabeth A. Weeks, “Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997,” *Food and Drug Law Journal* 54 (1999): 645-65, 645.

⁶¹ Opposition Comments at 9.

⁶² Opposition Comments at 10.

⁶³ Opposition Comments at 9-10.

⁶⁴ The first example offered by the Sponsor is the approval by FDA on September 10, 2001 of the combination of Xeloda (capecitabine) and Taxotere (docetaxel) for treating patients with metastatic breast cancer that has progressed after treatment with an anthracycline-containing cancer therapy. FDA initially approved Xeloda, an oral therapy, for the treatment of breast cancer on April 30, 1998, and FDA approved Taxotere, an intravenous product, for the treatment of advanced breast cancer on May 15, 1998. See FDA Press Release, “FDA Approves Xeloda in Combination with Taxotere for Advanced Breast Cancer” (Sept. 10, 2001) (available at: <<http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01101.html>>). Thus, when Xeloda and Taxotere are used together, each is being used for an FDA-approved use.

The Sponsor’s second example is FDA’s approval on July 15, 1999 of Actos to improve glycemic control in patients with Type 2 diabetes. Actos is indicated as a monotherapy and for use in combination with a sulfonylurea, metformin, or insulin “when diet and the single agent does not result in adequate glycemic control.” Letter, FDA/CDER to Mikihiro Obayashi, President, Takeda America Research & Development Center, Inc. (July 15, 1999). When used alone or together to treat Type-2 diabetes, each drug is being used for one of its FDA-approved indications.

Each example describes drug products that are being used in combination to treat indications approved for the single drugs at issue.

Upon close examination, the Sponsor's four examples underscore the fact that FDA's approval of mifepristone for use in combination with misoprostol, a drug never approved as an abortifacient, constitutes a significant departure from FDA precedents. As Professor Richard Merrill explained, "[i]n FDA's view, to promote any use of [its] new drug, the manufacturer must have agency approval – allowing that use to be included in the official labeling."⁶⁵ The approval in this instance struck at the heart of FDA's long-held policy that in order for a new drug use to be promoted, the drug's sponsor must submit an application seeking to demonstrate the safety and effectiveness of that new use.⁶⁶ It defies logic to imagine that Danco could be allowed to do with misoprostol what Searle could not do with its own drug – that is, promote an unapproved use of misoprostol. Yet, that activity is exactly what FDA permitted in Mifeprex's case. FDA's regulatory framework would be rendered toothless if third parties were permitted to behave in this manner.

In fact, Searle, which held the patent for misoprostol,⁶⁷ apparently *objected* to adding an indication for abortion to the Cytotec label. Searle's objections were overridden because only the combined regimen was effective. As the Sponsor explained, "[t]he fact is that mifepristone used as contemplated in 1983 was a failed drug – it was not sufficiently efficacious to have ever been approved."⁶⁸ Perhaps to avoid having to obtain Searle's cooperation, in an unprecedented

The Sponsor's third example is FDA's approval on October 26, 2001 of Viread (tenofovir disoproxil fumarate), a nucleotide reverse transcriptase inhibitor of HIV, for combined use with other antiretroviral agents for the treatment of HIV-1 infection in adults. The antiretroviral agents with which Viread is to be used have separately been approved for the treatment of HIV. Letter, FDA/CDER to Rebecca Coleman, Gilead Sciences, Inc. (Oct. 26, 2001) (NDA 21-356). The fact that Viread was not approved for use as a monotherapy in the treatment of HIV does not alter the analysis, but rather makes it a useful comparison for mifepristone, which has been approved as an abortifacient only in conjunction with misoprostol. Thus, when used together, each drug is being used for one of its FDA-approved indications.

The Sponsor offers as its fourth example FDA's approval of Nexium (esomeprazole magnesium) on February 20, 2001 for the treatment of erosive esophagitis and other symptoms associated with GERD (Gastroesophageal Reflux Disease). Letter, FDA/CDER to Kathryn D. Kross, AstraZeneca, LP (Feb. 20, 2001) (NDA 21-153; NDA 21-154). For one of its approved indications, *H. pylori* eradication, Nexium is used in combination with amoxicillin and clarithromycin, both of which have been approved for treating *H. pylori*. Thus, when they are used in combination with Nexium, each drug is simply being used for one of its approved indications.

⁶⁵ Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1766, n.40. As noted in the Petition, former FDA general counsel, Peter Barton Hutt, observed that FDA's actions with respect to misoprostol "set[] an extraordinary precedent" because FDA was "seemingly encouraging a drug's unapproved use." See Petition at 42-43 (Hutt's quotation was reported in Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1).

⁶⁶ A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

⁶⁷ The patent for misoprostol has since expired, but at the time the Mifeprex Regimen was approved, Searle held exclusive rights to that patent.

⁶⁸ Population Council Response to the Request for Revision of the Regulatory Review Period Determination for MIFEPREX[®] Submitted by Concept Therapeutics Inc., Docket No. 01E-0363 (July 2, 2002): at 3 ("Sponsor's

“joint decision” in July 1994, FDA and the Sponsor “determined that the NDA need not cover misoprostol as well as mifepristone.”⁶⁹ The Sponsor subsequently explained, however, that “there can be no doubt that the approved human drug product contemplates both mifepristone and misoprostol, as shown in the approved labeling,”⁷⁰ which “specifically states that administration of mifepristone must be followed by administration of misoprostol.”⁷¹ The Sponsor added that “FDA has made clear on numerous occasions, FDA review of an NDA is ‘inextricably intertwined’ with the proposed labeling for the product.”⁷² In so stating, the Sponsor speaks out of both sides of its mouth – acknowledging that combined use with misoprostol is necessary for Mifeprex’s effectiveness and labeling, but “agreeing” with FDA that a corresponding misoprostol approval is not necessary.

Conclusion

In summary, the inclusion of misoprostol in the Mifeprex Regimen, outside of the NDA approval process for misoprostol, was unlawful. In order to reverse the extraregulatory approval of misoprostol as an abortifacient, FDA must withdraw its approval of the Mifeprex NDA.

D. Mifeprex-Misoprostol Abortions Are Not Safe.

The Sponsor continued in its Opposition Comments to defend the safety of Mifeprex, but has not allayed the concerns set forth in the Petition.⁷³ Rather than address the scientific and medical issues raised in the Petition, the Sponsor has mischaracterized them. As discussed above, the trials submitted by the Sponsor to support its NDA did not establish the safety of mifepristone-misoprostol abortions, and post-approval data on the Regimen have done no better - serving only to raise the Petitioners’ concerns about the safety of the Mifeprex Regimen.

1. FDA Determined that Mifeprex Would Be Unsafe without Restrictions.

FDA approved mifepristone under the restricted distribution prong of Subpart H, which FDA reserves for drugs that “can be used safely only if distribution or use is modified or restricted.”⁷⁴ Accordingly, the Mifeprex Regimen includes a number of restrictions.⁷⁵ As the

Response to Corcept”). In this document, the Sponsor responded to Corcept’s June 10, 2002 request that FDA consider 1983 rather than August, 4, 1994 as the starting date for the regulatory review of the Mifeprex investigational new drug application (“IND”). The Sponsor sought to convince FDA that the appropriate period for determining patent length began on August 4, 1994, the date of the IND that allowed for the investigation of mifepristone plus misoprostol to induce abortions. The Sponsor did not obtain the patent extension that it sought. The initial ruling in the Population Council’s favor was reversed by FDA. *See Note, Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex; Amendment*, 67 Fed. Reg. 65358 (Oct. 24, 2002).

⁶⁹ Sponsor’s Response to Corcept at 2.

⁷⁰ Sponsor’s Response to Corcept at 3.

⁷¹ Sponsor’s Response to Corcept at 2.

⁷² Sponsor’s Response to Corcept at 2-3 (citation omitted).

⁷³ *See* Opposition Comments at 10-14.

⁷⁴ *Subpart H Final Rule*, 57 Fed. Reg. at 58942 (“Summary”).

Petition explained, however, these restrictions were inadequate to make the drug safe.⁷⁶ Moreover, the Sponsor never acknowledged the inherent dangers posed by the approved Mifeprex Regimen, balked at implementing distribution restrictions, and dismissed out of hand the challenges about the adequacy of the restrictions to reduce the dangers of the Mifeprex Regimen.⁷⁷ Now that it has FDA's imprimatur to market the drug, the Sponsor takes minimal, if any, actions to carry out the required restrictions.⁷⁸

Additionally, FDA's final decision to omit key restrictions from the approved Regimen has subjected patients who use the Mifeprex Regimen to unnecessary risks. A pre-procedure ultrasound, for example, is necessary to evaluate the gestational age because the Mifeprex Regimen has been shown to be less effective and riskier to the patient as gestational age increases.⁷⁹ Ultrasound is also necessary to identify women whose pregnancies are ectopic and who should not undergo the Mifeprex Regimen.⁸⁰ Further, because complications and failures are common and predictable and can seriously endanger the health of the patient, FDA should

⁷⁵ For a list of the restrictions, *see* Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 2 ("Mifeprex Approval Letter"). The Sponsor contends in its Opposition Comments that it cooperated with FDA by proposing restrictions. *See* Opposition Comments at 10-11. This contention reflects the Sponsor's failure to distinguish between restrictions on the distribution of a drug to prescribing physicians and restrictions designed to ensure patient safety. Furthermore, contrary to the Sponsor's suggestion that decisions about the restrictions in the Mifeprex Regimen were the product of "discussion, negotiation, give and take, debate, even on occasion disputes, between FDA and the Sponsors [that] is characteristic of the review process for many drugs" (Opposition Comments at 11), the Sponsor went to great lengths to avoid including safety restrictions in the Mifeprex Regimen. In fact, after the Sponsor failed to suggest appropriate restrictions to protect Mifeprex patients, FDA proposed its own set of restrictions. Then, the Sponsor complained publicly about the allegedly onerous restrictions. FDA relented and inappropriately eliminated a number of key restrictions. *See* Petition at 49-57 for a discussion of the development of and the Sponsor's opposition to safety restrictions.

⁷⁶ *See* Petition at 57-65.

⁷⁷ *See* Opposition Comments at 10. The Petition did not assert that the approved regimen must exactly follow the regimen employed during the trials. Nevertheless, if trials include important safeguards that are omitted from the approved regimen, then the relevance of the data generated by those trials is undermined. For this reason, a trial should be designed to reflect the anticipated conditions under which a drug will be used. *See* Petition at 75-76. For example, had the Sponsor designed the trial to reflect anticipated conditions of use, misoprostol probably would have been administered vaginally during the trials, which appears to be the standard method of administration now that the Mifeprex Regimen is approved. Had the trial protocol called for vaginal administration, it would have drawn attention to the unlawful inclusion of misoprostol in the Regimen because misoprostol is approved only for *oral* use. As FDA has explained, "[i]n order to change or add a new dosing regimen to the labeling, the sponsor must submit data to FDA from clinical trials that show the new regimen is safe and effective." *See* FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol virginally at different doses?") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm>).

⁷⁸ *See* Section I.D.3, herein.

⁷⁹ *See* Spitz Article at 1241 ("Results").

⁸⁰ The Sponsor's Opposition Comments addressed the use of ultrasound only for the purpose of dating pregnancies. As explained in the Petition, ectopic pregnancies cannot be treated by the Mifeprex Regimen and the symptoms of ectopic pregnancy are likely to be mistaken as the normal effects of undergoing a Mifeprex abortion. For a more complete discussion of the necessity of using ultrasound to identify ectopic pregnancies, *see* Petition at 60-61.

have required prescribing physicians to be trained in mifepristone-misoprostol administration and surgical abortions and to have *admitting* privileges at a nearby emergency facility.⁸¹

FDA determined that Subpart H restrictions were necessary because, without them, mifepristone-misoprostol abortions were not safe. Thus, the Petitioners' concerns with the Regimen's safety rest on the belief that the weakness of the Regimen's restrictions is inconsistent with FDA's decision to approve the drug under Subpart H.

2. Post-approval Evidence Confirms that the Approved Distribution Restrictions Were Insufficient to Adequately Protect Patients.

The Sponsor's analysis inaccurately characterized the post-approval experience with the Mifeprex Regimen.⁸² A number of life-threatening adverse events experienced by Mifeprex patients caused FDA to work with the Sponsor to issue a letter to health care providers.⁸³ The

⁸¹ In fact, FDA proposed to include such restrictions in the Mifeprex Regimen. The set of restrictions proposed by FDA on June 1, 2000, would have required physicians prescribing Mifeprex to be "trained and authorized by law" to perform surgical abortions, to be trained in administering the Mifeprex Regimen and handling resulting adverse events, and to have "continuing access (*e.g.*, admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility." See FDA, "FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00" (June 1, 2000) [FDA FOIA Release: MIF 000522]. See also American College of Obstetricians and Gynecologists, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000): at 1 (setting forth FDA's second proposed restriction, which is redacted in the publicly available copy of FDA's proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

⁸² Opposition Comments at 10, 13-14. The Sponsor pointed to a recent article authored by the medical director of Danco, Dr. Richard Hausknecht, as evidence that Mifeprex is safe. See Opposition Comments at 10 (citing Hausknecht Article); regarding Dr. Hausknecht, see also Petition at 71, n.309. Unfortunately, the article, which reports on the drug's use in the United States since approval, relies on data that are incomplete and of questionable quality. First, reliable data as to the number of patients who have undergone the Mifeprex Regimen is not available. Dr. Hausknecht used a figure of 80,000, which was derived from "sales figures [for Mifeprex] and known patterns of mifepristone utilization." Hausknecht Article at 464. This number may be too high as it may not take into account drugs that were ordered but not used. Second, the number of adverse events reported is likely to be significantly underestimated. Abortion clinics, which (according to Dr. Hausknecht's estimates) carried out approximately 90% of Mifeprex abortions, may have a disincentive to report adverse events from a procedure that they promote and may be less likely than physicians in private practice to report adverse events. In addition, it is likely that many patients were lost to follow up. In the U.S. Clinical Trial, 106 of the 2,121 patients (or nearly 5%) did not return for their third required visit. A higher "lost to follow up" number is to be expected outside of the clinical setting. Finally, the article's descriptions of the adverse events that were reported generally appear to be incomplete and tend to downplay any possible connection with the Mifeprex Regimen. For example, the article explained that a twenty-one year old woman had suffered a coronary artery occlusion five days after she received misoprostol. See Hausknecht Article at 464, col. 2. The article provided few details about her Mifeprex abortion and pointed to her "strong family history of heart disease" without also mentioning that there are no data on the safety of the Mifeprex Regimen in women with cardiac problems and these women were excluded from the Clinical Trials. In sum, an objective assessment of the safety and efficacy of mifepristone-misoprostol abortions would require a concurrently-controlled, randomized comparison of a mifepristone-misoprostol regimen reflecting actual conditions of use with surgical abortion. The Sponsor did not conduct or provide data from such trials in support of its application and Dr. Hausknecht's article – a very general overview without the first-hand, patient-level detail necessary to scientifically assess the safety of the Mifeprex Regimen – does not fill this void.

⁸³ Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) ("Dear Doctor Letter") (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>).

Petition discussed these life-threatening adverse events which included ruptured ectopic pregnancies, serious systemic bacterial infections, and a coronary event.⁸⁴ The Sponsor, in its Opposition Comments, insisted that “FDA has not found any causal connection” between the Mifeprex Regimen and these adverse events.⁸⁵ However, the clear implication of the issuance of the Dear Doctor Letter and FDA’s accompanying “Questions and Answers” is that such a causal link does exist.

The serious adverse events reported to date are consistent with concerns about the drug regimen that were expressed prior to the approval.⁸⁶ The recent death of Holly Patterson, an eighteen year old from Livermore, California, unfortunately epitomizes the concerns of the Petitioners.⁸⁷ According to Ms. Patterson’s father, at the time of his daughter’s death, she was terminating her pregnancy with a Mifeprex Regimen prescribed by the Planned Parenthood in Hayward, California. Apparently, Ms. Patterson started the abortion procedure on Wednesday, September 10, 2003, by taking mifepristone tablets. On Saturday, September 13, 2003, she apparently took the misoprostol that the clinic had given her. By Sunday she was having such severe cramping and bleeding that her boyfriend took her to the emergency room. Ms. Patterson received pain killers and was sent home, but she continued to bleed severely and experienced acute pain that prevented her from walking. Early Wednesday, September 17, 2003, Ms. Patterson’s boyfriend took her back to the emergency room, where she died that afternoon.

According to Mr. Patterson, the doctor told him that his daughter “hadn’t aborted all the fetus, and she had fragments left in her, and she had a massive systemic infection and went into septic shock.”⁸⁸ The results of the coroner’s investigation are not expected to be released for several months, but Ms. Patterson’s apparent death of a serious systemic bacterial infection is not the first such death since FDA approved Mifeprex. As noted above, the Dear Doctor Letter

⁸⁴ See Petition at 65-71. As the number of mifepristone-misoprostol abortions rises, the number of serious adverse events associated with these abortions is likely to increase as well. Because the normal progression of the Mifeprex Regimen is characterized by prolonged bleeding, the patient bears the responsibility for determining how much bleeding is excessive and whether she needs to seek medical assistance. Health care providers who are not experienced providers of abortion, generally, or mifepristone-misoprostol abortions, specifically, may be poorly equipped to assist the patient in determining whether medical intervention is necessary, let alone to provide the needed medical intervention.

⁸⁵ See Opposition Comments at 13.

⁸⁶ See *Americans United for Life et al.*, Citizen Petition (Feb. 28 1995) (requesting FDA’s consideration of a number of potential hazards of mifepristone-misoprostol abortions) [FDA FOIA Release: MIF 006144-6248].

⁸⁷ Julian Guthrie, “Pregnant Teen’s Death Under Investigation; East Bay Woman Had Taken RU-486, According to Father,” *San Francisco Chronicle* (Sept. 19, 2003): at A21 (available at: <http://www.sfgate.com>). See also Gina Kolata, “Death at 18 Spurs Debate Over a Pill for Abortion,” *New York Times* (Sept. 24, 2003): at A24 (“There were 264 adverse reactions, including infections, bleeding, allergic reactions and tubal pregnancies.”).

⁸⁸ *Id.* See also Julian Guthrie, Sabin Russell, and Katherine Seligman, “After Daughter’s Death, Father Wants Close Look at RU-486; Abortion Pill’s Safety Defended by Doctors as Better than Surgery,” *San Francisco Chronicle* (Sept. 20, 2003): at A17 (available at: <http://www.sfgate.com/cgi-bin/article.cgi?file=/chronicle/archive/2003/09/20/BA310011.DTL>) (“Patterson said the attending physician at Pleasanton’s Valley Care Medical Center told him his daughter had died of septic shock – a severe bacterial infection. ‘The doctor told me she had fragments of the fetus still left in her uterus and that caused the infection.’”).

reported “[t]wo cases of serious systemic bacterial infection (one fatal).”⁸⁹ The presence of retained products of conception can lead to the development of intrauterine or systemic infection, and it is possible that mifepristone could potentiate this possibility via negative effects on immune system function or normal protective mechanisms.⁹⁰

In addition to questions about Mifeprex causation in this case, questions also have been raised about the role that Ms. Patterson or her local hospital emergency room may have played in contributing to her death.⁹¹ These questions cannot be answered without recognizing that patients and emergency room physicians may be unable to distinguish the normal progress of the Regimen from a life-threatening situation. Consequently, it is not at all clear that emergency rooms will be able to rescue dangerously ill Mifeprex patients from the peril in which they have been placed by the Regimen. Consider the plausible scenario described in the footnote below.⁹² The severity of the reported adverse events requires FDA action to remove Mifeprex from the market.

⁸⁹ Dear Doctor Letter at 1. The fatality apparently precipitated a halt in the Population Council’s clinical trials of mifepristone in Canada.

⁹⁰ Given the nature of the Mifeprex Regimen, the embryo or other products of conception will not be expelled from the uterus in a number of cases. It is well known that the presence of retained necrotic products of conception can lead to intrauterine and systemic infection. Furthermore, it is possible that mifepristone itself may alter the local immune response at the level of the endometrium or the cervix. There are numerous alterations of the immune system during pregnancy, and progesterone can affect immune system function. Therefore, it is plausible that a progesterone receptor antagonist like mifepristone could negatively affect the normal immune system within the uterus, or compromise antibacterial mechanisms of the cervix, making a woman more susceptible to infection. *See, e.g.,* World Health Organization (WHO), “Pregnancy Termination with Mifepristone and Gemeprost: A Multicenter Comparison between Repeated Doses and a Single Dose of Mifepristone,” 56 *Fertility & Sterility* 32-40 (1991) (29.4% of patients with incomplete abortion compared with 2.6% of those with complete abortion received antibiotics during a six week follow-up period for suspected genitourinary infection; both groups combined accounted for 3.9% of the total study population).

⁹¹ *See, e.g.,* Gina Kolata, “Death at 18 Spurs Debate Over a Pill for Abortion,” *New York Times* (Sept. 24, 2003): at A24 (“But it is unclear what happened to Holly Patterson. Did she have enough medical supervision while taking the pills? When did she seek medical attention? Did she wait until it was too late? Did she tell the doctors in the emergency room that she had taken mifepristone? Why, in fact, did she die?”).

⁹² A patient comes to the emergency room complaining of significant pelvic pain and cramps. She reports that she has taken Mifeprex and misoprostol for a medical abortion. At this time, she has no significant change in vital signs (*i.e.*, no fever or very low grade fever – which can be related to misoprostol – and no significant tachycardia, etc.). The emergency room physician, knowing that this drug combination normally causes cramping at this stage in the process, assumes she has a personal low pain tolerance threshold, and, therefore, gives her pain medications to try to alleviate her discomfort until the abortion completes. However, the patient may be in the early stage of an intrauterine infection even though she is not yet manifesting other signs of that condition aside from pain and bleeding which are both part of the Mifeprex abortion process. At this stage, the emergency room physician has no good way to detect that an infection has begun. Furthermore, even if the emergency room physician found evidence of retained tissue in the uterus, the physician would not be surprised or alarmed by that discovery given the nature of mifepristone-misoprostol abortions. Unless the patient had significant hemorrhaging or evidence of infection, no intervention would be necessary or even warranted since one would presume that the abortion was going according to plan at that juncture (recall that bleeding can last up to several weeks duration). So to continue this hypothetical scenario, the patient goes home, and the infection subsequently becomes systemic. The patient goes into septic shock and is not able to be saved by the time she re-presents to the emergency room. It would not be surprising if Ms. Patterson’s death followed such a course given statements made to the press by her father. In this credible scenario the Mifeprex Regimen, after having placed her in great danger, effectively camouflaged the seriousness of her condition from the emergency room physician.

Furthermore, FDA cannot rely on the “spotty” reporting of adverse events for the Mifeprex Regimen. The usual flow of post-approval adverse event information will not be forthcoming for this drug. It is questionable whether individual lawful distributors of Mifeprex, who tend to be outside the mainstream pharmaceutical wholesale distribution industry, will routinely report adverse events to FDA.⁹³ Also, because the drug is intended to be administered in physicians’ offices, a pharmacist is unlikely to dispense the product or hear of drug-drug and drug-food interactions, or other adverse events. Moreover, the types of facilities that provide medical and surgical abortions are often staffed with social-work counselors and health care workers who are not medical doctors and have limited medical training. As such, they may be unfamiliar with the adverse event reporting procedure for medical professionals (*i.e.*, MedWatch).

Even for properly-licensed physicians, FDA’s MedWatch reporting is voluntary.⁹⁴ Since privacy issues are often the primary concern of women who seek abortions, a physician may not file a MedWatch report in order to protect patient confidentiality. Accordingly, the Petitioners are concerned about the possibility that medical complications are not being reported. Finally, it is possible that other women who have suffered adverse events during a mifepristone-misoprostol abortion have sought assistance from crisis pregnancy centers, counselors, and charitable organizations,⁹⁵ which may not be familiar with the MedWatch reporting system. Given the foregoing, the Petitioners believe that FDA’s continuing review of the safety profile of Mifeprex relies improperly on an incomplete database of post-approval adverse events.

3. The Sponsor Has Failed to Require Adherence to the Restrictions.

The Sponsor insisted that it “will continue, as [it] always intended, to honor [its] commitments to carry out the program of restrictions imposed in the approval letter.”⁹⁶ Yet, the Sponsor has broken its promise. The Sponsor apparently has not taken steps to ensure that Mifeprex is used in accordance with the approved Regimen and has continued to distribute the drug to providers that depart from the Mifeprex Regimen. For instance, the Sponsor has asserted, in its Opposition Comments, the erroneous position that the guidelines in the Prescriber’s Agreement “do not state any specific dose or regimen for prescribing Mifeprex”⁹⁷ The Sponsor’s statement reflects only one example of its continuing refusal to accept even FDA’s minimal restrictions issued pursuant to Subpart H.

⁹³ Obviously, distributors of mifepristone who are outside the lawful channels of distribution are even less likely to report adverse events.

⁹⁴ See <<http://www.fda.gov/medwatch/report/hcp.htm>>.

⁹⁵ *Consider Estate of Brenda Vise vs. Volunteer Women's Medical Clinic, L.L.C., et al.* (Circuit Court of Hamilton County, Tennessee, filed August 14, 2002); *Danlin Tang, Albert Ng vs. Dr. Soon Chon Sohn, Family Planning Associates Medical Group, and Does 1 – 50* (Superior Court of the State of California for the County of Los Angeles, Central District, notice to file dated December 13, 2002).

⁹⁶ Opposition Comments at 6.

⁹⁷ Opposition Comments at 14.

In the face of this recalcitrance, FDA should exercise its enforcement authority, investigate the Sponsor's failed commitments under its NDA approval, and take appropriate action, as it has in other cases where risk management programs were deemed insufficient to protect patients.⁹⁸ We note that, contemporaneous with the issuance of the Sponsor's Dear Doctor Letter, FDA underscored the possibility that if providers "do not follow the agreement, the distributor may discontinue distribution of the drug to them."⁹⁹ Shortly after approving Mifeprex, the Agency wrote to a member of Congress and stated, "If restrictions are not adhered to, FDA may withdraw approval."¹⁰⁰

Even assuming that the Sponsor's responsibilities extend only as far as ensuring that the prescriber is adhering to the Prescriber's Agreement, the Sponsor is failing to meet its due diligence obligation.¹⁰¹ The Prescriber's Agreement requires, *inter alia*, that the prescriber "must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself."¹⁰² The Patient Agreement, which both the patient and the prescriber sign, states that the patient "believe[s] I am no more than 49 days (7 weeks) pregnant."¹⁰³ Yet numerous prescriber websites advertise the Mifeprex Regimen as being available for patients whose pregnancies have progressed beyond 49 days.¹⁰⁴ The Patient

⁹⁸ For example, GlaxoSmithKline voluntarily withdrew its NDA for Lotronex (alosetron hydrochloride) rather than accept restrictive risk management guidelines involving informing patients of risks, limiting access to closely monitored patients, and continued clinical research. See "FDA and Glaxo Still Working on Lotronex's Return," *Dickinson's FDA Webview* (Jan. 24, 2002). Bayer voluntarily withdrew Baycol (cerivastatin) after reports of deaths due to severe rhabdomyolysis, when risk management efforts of labeling changes and "Dear Healthcare Provider" letters had little impact on physicians who continued to prescribe the drug at unrecommended higher doses. See "31 Baycol-related Deaths Cause the Drug's Withdrawal," *Dickinson's FDA Webview* (Aug. 8, 2001). Warner Lambert withdrew Rezulin (troglitzone) at FDA's urging after label restrictions and recommended monitoring of liver function failed to control inappropriate prescribing. See "Rezulin Withdrawal a Defeat for FDA 'Labeling Can Do It' Theory," *Dickinson's FDA Webview* (Mar. 21, 2000).

⁹⁹ See FDA Q & As at Question 12.

¹⁰⁰ See Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

¹⁰¹ See Opposition Comments at 14-15.

¹⁰² Mifeprex™ (Mifepristone) Tablets, 200 mg Prescriber's Agreement ("Prescriber's Agreement").

¹⁰³ See Item 4 of the Patient Agreement Mifeprex (mifepristone) Tablets ("Patient Agreement"). In addition, the Mifepristone Medication Guide ("Medication Guide") states that you should not take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began."

¹⁰⁴ See, e.g., All Women's Health Centers website (available at: <http://www.floridaabortion.com/services_abortion/nonsurgical.shtml>) (visited Sept. 5, 2003) ("Non-surgical abortions, sometimes called 'medical abortions,' are performed in the first 9 weeks of pregnancy. Non-surgical abortion can be administered in pill form (otherwise known as Mifeprex or RU-486)."); Family Planning Associates Medical Group, Phoenix and Tempe Arizona, (available at: <<http://www.fpamg.com/medical.html>>) (visited Sept. 5, 2003) (noting that Mifeprex Regimens are "done until the 56th day of pregnancy"); Planned Parenthood Golden Gate (available at: http://www.ppgg.org/medical/abortion_medical.asp) (visited Oct. 1, 2003) ("Medical abortion is a way to end pregnancy without surgery. It is done with medications up to 63 days after the last period begins."); Seattle Medical and Wellness Clinic (available at: <<http://www.smawc.com/html/services.html>>) (visited Sept. 5, 2003) (including following description: "Medical Abortion (9 weeks LMP or less): We offer non-surgical abortion with Mifeprex (a.k.a. the Abortion Pill, RU486) and Cytotec (misoprostol).").

Agreement also states that the patient “will take misoprostol in [her] provider’s office two days after [she] take[s] Mifeprex (Day 3).”¹⁰⁵ Yet many prescribers’ websites indicate that patients take misoprostol at home rather than at the provider’s office.¹⁰⁶ The discrepancies between the marketplace regimen being prescribed and the approved Regimen that the patient agrees to follow indicate that many prescribers are allowing patients to make false statements. Under its NDA duties, the Sponsor has an obligation to conduct due diligence about the prescribers to whom it sells Mifeprex, and it must stop those sales if the approved Regimen is breached. Furthermore, the Sponsor has a duty to keep records of these stopped distributions.¹⁰⁷

Given that these discrepancies are freely published on prescriber websites, the Sponsor should be aware of them.¹⁰⁸ Therefore, the Sponsor knowingly continues to supply prescribers who are not following the guidelines in the Prescriber’s Agreement. These prescribers are knowingly eviscerating the requirements to provide patients with the Medication Guide, to

¹⁰⁵ See Patient Agreement, Item 6. In addition, the Medication Guide states that the patient “**must return** to [her] provider on Day 3 and about Day 14” (emphasis in original).

¹⁰⁶ See, e.g., Family Planning Associates Medical Group, Phoenix and Tempe Arizona, (available at: <<http://www.fpamg.com/medical.html>>) (visited Sept. 5, 2003) (explaining that “[t]he patient inserts 4 tablets of Misoprostol into the vagina at home 2-3 days” after ingestion of Mifeprex); Little Rock Family Planning website <<http://www.lrfps.com/RU486.html>> (visited Sept. 5, 2003) (describing the regimen employed by the clinic, which is “one of these regimes [sic] which has been shown to be safe and is more convenient for women using the method”: “**Step Two, at home (or motel)** ... Six to 8 hours after the mifepristone pills have been swallowed 8 Cytotec tablets are placed in the vagina. **Step Three, this will depend on how far you live from our clinic:** A) *If you live within one hour of Little Rock* ... If you have not passed the pregnancy by 24 hours after you put the Cytotec tablets in your vagina, you will put a [sic] 4 tablets in your vagina and still plan to keep your appointment for the following week. B) *If you live outside the Little Rock Area* ... You will return at 9AM the following morning to have an ultrasound to see if the abortion is complete. If the abortion is complete you will be discharged home and asked to take a urine pregnancy test in 3 weeks. ... If you have not had a complete abortion you will be given 4 Cytotec [sic] to place in your vagina”); Planned Parenthood Golden Gate (available at: <http://www.ppgg.org/medical/abortion_medical.asp>) (visited Oct. 1, 2003) (“Medical abortion using Mifepristone involves three steps. First, the doctor will give you mifepristone pills, which block progesterone, a hormone needed to maintain pregnancy. Two days later, as directed by your clinician, you will insert another medication called misoprostol as a vaginal suppository. Misoprostol causes the uterus to contract and empty which completes the abortion. Finally, women must return to the clinic a few days after taking the misoprostol for a follow-up.”); Women’s Health Practice website (available at: <<http://www.womenshealthpractice.com/abortion.htm>>) (visited Sept. 5, 2003) (explaining, as part of the medical abortion regimen that the clinic describes as “most similar to the FDA-approved regimen,” that “[t]he misoprostol will be provided to you with medication instructions that carefully explain the timing and route of administration.”).

¹⁰⁷ 21 C.F.R. § 314.81(b)(2) (requiring NDA sponsors to submit an annual report describing distribution data). State or federal agencies may need these data if patient deaths continue and the public outcry (and/or the plaintiffs’ lawyers bar) demand investigations.

¹⁰⁸ The Petition set forth a number of examples of Mifeprex provider websites that advertised noncompliance with the approved Mifeprex Regimen. See Petition at nn. 309, 313, 315, 317. Since the submission of the Petition, these websites have not been altered. (These websites were visited most recently on September 5-7, 2003. One of the website addresses changed and its content was updated, but it still states that “at home, the patient will insert four tablets [of misoprostol] into her vagina.” See <http://www.presidentialcenter.com/services_nonsurgical.html> (visited Sept. 7, 2003)). It appears, therefore, that the Sponsor, alerted by the Petition to these instances of noncompliance, has not taken any steps to require compliance with the approved regimen. Dr. Hausknecht, the medical director of Danco, operates one of the websites that continues to advertise a regimen that differs from the approved regimen. See <<http://www.safeabortion.com/procedure.htm>> (visited Sept. 7, 2003).

obtain their signatures on the Patient Agreement, and to give them the opportunity to read and discuss these documents. The Patient Agreement is intended by FDA to describe the Mifeprex Regimen as approved and to obtain the patient's informed consent to adhere to the approved Regimen, all for the protection of the patient. Instead, some prescribers, with the Sponsor's tacit approval, are permitting patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements. In the face of such evidence, the Sponsor cannot be described as meeting its obligations with respect to the restrictions on Mifeprex.

Conclusion

Women are being told that Mifeprex is safe even if it is used in a manner different from the Regimen approved by FDA. This is a cavalier approach to distributing a drug that was deemed by FDA to be too dangerous to approve without restrictions. The Sponsor's refusal to restrict distribution to physicians who adhere to the approved Regimen represents the continuation of a pattern of overlooking the risks to women's health posed by Mifeprex. FDA should halt the marketing of this unsafe drug.

E. The Sponsor's Revised Phase IV Commitments Are Inadequate.¹⁰⁹

The Sponsor's Opposition Comments downplayed the significance of the changes prior to approval in the Sponsor's Phase IV commitments.¹¹⁰ As noted in the Petition, those changes by the Sponsor relegated certain study objectives to secondary status, eliminated the commitment to study the long-term effects of multiple uses of the Regimen, and weakened the commitment to monitor the adequacy of the distribution and credentialing system.¹¹¹

The Sponsor's insistence that the range of topics to be studied was not narrowed contradicts statements made by the Sponsor when it proposed modifications of its Phase IV commitments in September 2000.¹¹² The Sponsor, citing feasibility concerns, decided not to study the long-term effects of multiple uses of the Mifeprex Regimen.¹¹³ Moreover, combining multiple study objectives into one study reduced the value of the data that would be generated

¹⁰⁹ The Petitioners requested, pursuant to FOIA, information about the Phase IV Mifeprex study protocols and any data arising from the Phase IV studies submitted by the Sponsor. *See* FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001). To date, the Petitioners have not received any responsive information.

¹¹⁰ *See* Opposition Comments at 15-16. *See also* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 15, 2000): at 1 [FDA FOIA Release: MIF 001326] (committing to conducting two Phase IV studies).

¹¹¹ *See* Petition at 84-88.

¹¹² *See* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 5 [FDA FOIA Release: MIF 001333-49] ("As new data have become available, some of the studies originally proposed have become unnecessary. Other studies, on reflection, seem unlikely to gather useful data at any reasonable cost or, in some cases, at any cost.").

¹¹³ *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 7 ("Mifeprex Approval Memo"). As discussed in the Petition, the Sponsor, in asking for the elimination of this commitment, was motivated in part by concerns that conducting such a study would be burdensome for the Sponsor – a reason that is not generally persuasive with FDA. *See* Petition at 87.

with respect to the secondary study objectives.¹¹⁴ Given the importance of understanding the effect of a patient's age, the effect of a patient's smoking status, the rate of patient follow-up on Day 14, and the adequacy of the distribution and credentialing system, the Sponsor should not have been permitted to accord these study objectives secondary status.

The Sponsor defended the changes in the study requirements by citing FDA's approval memorandum for the proposition that the changes in the Phase IV Study commitments reflected changes to the distribution system and labeling.¹¹⁵ The Sponsor's argument is misleading. By allowing the distribution of mifepristone to physicians who could not provide surgical intervention, an immediate need arose to study the effect of that major change;¹¹⁶ accordingly, FDA added a primary study requirement.¹¹⁷ However, the September 2000 changes in distribution and labeling should have not have reduced or eliminated other primary Phase IV study commitments that were not related to the distribution or labeling changes.

Conclusion

FDA inappropriately granted the Sponsor's request to reduce its original Phase IV commitments. As a consequence, key questions about the safety of the Mifeprex Regimen will remain unanswered.

F. The Approval of Mifeprex Without Supporting Pediatric Data Was Both Unlawful And Imprudent.

In its Opposition Comments, the Sponsor admitted that it did not conduct clinical studies in the pediatric population, but relied instead on an FDA "waiver" of pediatric testing. Yet, the FD&C Act and FDA's approval regulations for NDAs require safety and effectiveness testing to support a new drug's indications for use. In a case where the Sponsor does not intend to restrict the drug's use in the pediatric population, FDA has only limited authority to cede the requirement for pediatric testing. In the case of Mifeprex, FDA's decision to approve the NDA without pediatric data was arbitrary, capricious and unlawful agency action.

¹¹⁴ Specifically, the effects of age and smoking status and the frequency with which patients return for follow-up on Day 14 were to be studied as part of "[a] cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compare to physicians who refer their patients for surgical intervention." See Petition at 86 (citing Mifeprex Approval Letter at 3). Furthermore, this study would be the only Phase IV study of another objective originally slated to be the focus of a separate Phase IV study, namely the adequacy of the distribution and credentialing system. See generally Mifeprex Approval Memo at 7.

¹¹⁵ See Opposition Comments at 15-16 (citing Mifeprex Approval Memo at 7).

¹¹⁶ This change was deemed significant enough to require the addition of a "black box" warning to physicians who could not perform surgical abortions. The black box warning directed them to make arrangements for the provision of emergency surgical intervention.

¹¹⁷ FDA correctly noted the need for a new study objective when it approved this change: "To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study." Mifeprex Approval Memo at 5.

1. FDA's NDA Approval Regulations Required Pediatric Data.

The law is clear that the clinical studies used to support an NDA must establish the drug's safety and efficacy for the proposed conditions of use. Under the FD&C Act, a person may file an NDA requesting FDA approval of a new drug provided that the NDA contains, in relevant part, "full reports of investigations which have been made to show whether or not such drug is safe *for use* and such drug is effective *in use*" ¹¹⁸ Likewise, FDA's NDA approval regulations require "a description and analysis of each controlled clinical study *pertinent to a proposed use* of the drug." ¹¹⁹ This testing requirement exists separately from the so-called "Pediatric Rule," ¹²⁰ which also delineates pediatric testing requirements.

The Petitioners acknowledge that, as of October 17, 2002 and for the time being, FDA is enjoined from enforcing the Pediatric Rule. ¹²¹ However, the Petitioners challenge the Sponsor's contention that the issue of FDA's proper administration of the Rule is moot, in light of the AAPS court's decision to grant an appeal of the case, which is now pending. ¹²² Rather, the Mifeprex NDA was subject to the Pediatric Rule, which was finalized and became effective while FDA was reviewing the NDA, ¹²³ and FDA should have administered it properly ¹²⁴ or waived it properly. ¹²⁵

¹¹⁸ 21 USC § 355(b)(1)(A) (emphasis added).

¹¹⁹ 21 C.F.R. § 314.50(d)(5)(ii) (emphasis added).

¹²⁰ See Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (testing requirements set forth in 21 C.F.R. § 314.55). See also Petition at 76-83 (discussing Pediatric Rule).

¹²¹ *Association of American Physicians and Surgeons v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002) ("AAPS").

¹²² The Elizabeth Glaser Pediatric AIDS Foundation and the American Academy of Pediatrics filed a motion to appeal on December 16, 2002. See Docket for Case No. 00-CV-2898 (entry no. 73).

¹²³ The Pediatric Rule was promulgated on December 2, 1998 and became effective on April 1, 1999. FDA reviewed the Mifeprex NDA from March 18, 1996 until September 28, 2000, when it was approved.

¹²⁴ Under the Pediatric Rule, FDA's treatment of the Mifeprex NDA was improper, in part, because the agency did not require the Sponsor to submit supporting pediatric data. The regulation stated that, "where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults *usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.*" 21 C.F.R. § 314.55(a) (emphasis added). This requirement also was articulated earlier by FDA in the Prescription Labeling regulation. See 59 Fed. Reg. 64240 (Dec. 13, 1994); 21 C.F.R. § 201.57(f)(9)(iv). As noted elsewhere in this Response, the Petitioners also question whether the Sponsor's adult data were derived "from adequate and well-controlled studies."

¹²⁵ It should be noted that even if FDA concluded that pediatric effectiveness of the Mifeprex Regimen could be extrapolated from adult studies, this would not be an appropriate ground for an actual *waiver* of the Pediatric Rule. The Pediatric Rule provides three grounds for waiver from the obligation imposed by the rule on drug sponsors to demonstrate that their drug is safe and effective for pediatric patients. 21 C.F.R. § 314.55(c). In some instances, drug sponsors are able to provide sufficient adult data, usually supplemented by pediatric-specific data, from which pediatric safety and efficacy can be extrapolated. 21 C.F.R. § 314.55(a). FDA stated that it was waiving the pediatric rule with respect to Mifeprex, yet did not cite to any of the bases for waiver provided in paragraph (c) of the Pediatric Rule. Mifeprex Approval Letter at 3. For a comprehensive discussion on the ineligibility of Mifeprex for a waiver from the Pediatric Rule, see the Petition at 78-82.

Irrespective of the current status of the *AAPS* case, at the time of the approval of the Mifeprex NDA the Agency was obligated to meet the requirements of its NDA approval regulations. FDA erred in its failure to require the Sponsor to submit pertinent pediatric data and to assess those data in its review of the NDA for Mifeprex. In so doing, the Agency abrogated its role of protecting and promoting the public health and safety. This constitutes the type of “arbitrary and capricious” action that is generally prohibited under the Administrative Procedures Act (“APA”).¹²⁶

2. The Drug’s Expected Conditions of Use Included the Pediatric Population.

Mifeprex is intended for use by menstruating females. The drug’s labeling states “Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days’ pregnancy.” Nothing in the “Indication and Usage” section of the labeling limits the drug’s use to adults.¹²⁷ Likewise, Danco’s marketing claims are not targeted to a particular age group, such as women “over age 18.” The patient population therefore logically includes all females who can become pregnant – that is, as of the age their first menstrual period begins (*i.e.*, “menarche”) until they no longer have a menstrual period (*i.e.*, “menopause”). According to FDA, the average age of menarche in the United States is 12 years, although menstruation may commence in healthy females as early as age 10.¹²⁸

Under the pediatric labeling regulations, the Agency defines “pediatric population(s)” and “pediatric patient(s)” as the age group “from birth to 16 years, including age groups often called ... adolescents.”¹²⁹ Therefore, the population of menstruating females (*i.e.*, 10 or 12 and older) and the pediatric population (*i.e.*, up to 16) overlap by up to 6 years. Based on Danco’s labeling and marketing to the menstruating female population without any age restriction, pediatric use of this product was clearly contemplated. Because Mifeprex will be used by some number of adolescent girls who become pregnant, FDA should have required the Sponsor to produce safety and effectiveness data for the pediatric population.

3. FDA Should Have Required the Submission of Pediatric Study Data Prior to Approving Mifeprex.

Under its broad authority granted by the FD&C Act, not only may FDA require the submission of pediatric data as part of a product’s NDA, but the Agency *must* require such data when the product’s conditions of use warrant pediatric testing. However, the Agency approved

¹²⁶ 5 USC § 706(2)(A).

¹²⁷ Instead, the drug’s labeling contains one non-constructive statement in the “Precautions” section of the labeling: “Safety and effectiveness in pediatric patients have not been established.” Given the logical reading of the drug’s indication and the medical information on the age range of menstruation, this one sentence in a package insert of 15 pages is valueless.

¹²⁸ See *On the Teen Scene: A Balanced Look at the Menstrual Cycle*, FDA Consumer Magazine (Dec. 1993) (available at: <http://www.fda.gov/fdac/reprints/ots_mens.html>). In the U.S., the average age of the start of menopause is 51. See *Taking Charge of Menopause*, FDA Consumer Magazine (Nov.-Dec. 1999) (available at: <http://www.fda.gov/fdac/features/1999/699_meno.html>).

¹²⁹ 21 C.F.R. § 201.57(f)(9).

Mifeprex without requiring the Sponsor to submit pediatric data or, apparently, any review of the pertinent scientific literature. When approving Mifeprex based solely on the data submitted in the NDA (*i.e.*, studies conducted in an adult population), FDA made the unsupported assumption that younger females (*i.e.*, children and adolescents) would have the same physiological response to this product as adult females.¹³⁰ Specifically, the Sponsor cited FDA's conclusion that "the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those of the age of 18 ...," despite the Agency's concession that most of the available data are from women 18 years and older.¹³¹ Further, the Sponsor noted that FDA has not found any "biological reason to expect that menstruating females under age 18 to have a different physiological outcome with the regimen."¹³²

As stated in the Petition, however, FDA's conclusion misreads the science. To assume, without specific data, that the effects of a potent antiprogesterone and a powerful prostaglandin analogue in pregnant adults will be the same for adolescents who are still developing in their physiologic, anatomic, and reproductive functions, is medically unsound. The relevant scientific evidence suggests that an assumption *cannot* be made that the effectiveness or safety of Mifeprex for adolescent girls is the same as for fully-developed adult women. Therefore, FDA's decision to the contrary lacks a sound and justified scientific basis.

Moreover, the Agency decision disregards decades of its own medical judgment. In the past, FDA has said that drugs should be studied directly in the pediatric population because "the action and adverse actions of pharmaceutical agents will vary as absorption, distribution, metabolism, and excretion, and receptor sensitivity are altered by the changes associated with growth and development."¹³³ For Mifeprex, these factors were not directly studied in children.

Studying the subpopulation of adolescents is even more important, according to FDA. For example, "[t]he development of puberty and the known effects of sex hormones on drug metabolism warrant consideration in drug evaluation in the adolescent."¹³⁴ Other "special problems" arise from the intense concern with self-image, leading to increased use (both admitted and denied) of prescription and over-the-counter drugs, dietary supplements, and cosmetics for such purposes as altering physical growth and sexual development, regulating mood and behavior, and influencing physical appearance.¹³⁵ FDA did not require a review of these adolescent-specific considerations with respect to the Mifeprex Regimen.

¹³⁰ See Mifeprex Approval Memo at 7.

¹³¹ Opposition Comments at 15 (citing FDA, "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments," at 28).

¹³² Opposition Comments at 15 (citing Mifeprex Approval Memo at 7).

¹³³ FDA Guidance for Industry, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children" (Sept. 1977), at 6 (hereafter, "Pediatric Study Guidance").

¹³⁴ Pediatric Study Guidance at 15.

¹³⁵ See Pediatric Study Guidance at 16-17.

In addition, FDA has said previously that a drug's safety profile may be different for adolescents because "medication may not be taken as prescribed. The adolescent frequently omits doses of medication, takes it at erratic intervals, and may take more than prescribed. Safety considerations should be addressed not only to the therapeutic dosage, but also to the consequences of suboptimal dosage and overdosage."¹³⁶ Given the two-drug-regimen and three-doctor-visit administration of the Mifeprex Regimen, a study of patient compliance issues in adolescents was warranted.

Conclusion

In summary, it is logical to conclude that Mifeprex is intended for use by a female population that, under the pertinent definitions adopted by FDA, includes pediatric females. Therefore, FDA should have required the submission of pediatric data with the NDA. Without any consideration of pediatric data, FDA's approval of Mifeprex is an abrogation of its fundamental duty to conduct the drug approval process in a way that protects and promotes the public health and safety. In so doing, the Agency acted in a way that was arbitrary, capricious, and contrary to law and its own regulations.

II. FDA Is Both Statutorily Empowered and Obligated to Grant an Administrative Stay of the Mifeprex NDA Approval.

The Sponsor's Opposition Comments contain three technical objections to the request for an administrative stay of the Mifeprex NDA approval.¹³⁷ First, the Sponsor alleges that an administrative stay is not the appropriate method by which FDA could withdraw the Mifeprex NDA. Second, the Sponsor alleges that the request is "untimely" because it was not filed within 30 days of the effective date for the Mifeprex NDA approval. Third, the Sponsor makes a general allegation that the Petitioners do not meet the criteria for an administrative stay under FDA's regulations. As described below, these allegations stem from an incorrect and overly restrictive reading of the Petitioners' request. Instead of answering the serious substantive issues raised in the Petition, the Sponsor has focused on the way in which the Petitioners framed their request for FDA action. Even more disconcerting, the Sponsor asks FDA to place administrative procedures above the Agency's statutory obligation to protect the public health.

A. FDA Has the Statutory Authority to Suspend the Mifeprex NDA Pending the Outcome of a Decision to Withdraw the Application.

The Petitioners' request for administrative stay of the Mifeprex NDA approval is equivalent to a request for FDA to use its authority under section 505(e) of the FD&C Act to "suspend the approval of [the] application immediately."¹³⁸ The FD&C Act states that an NDA may be "suspended" whenever FDA makes a finding of "imminent hazard to the public

¹³⁶ Pediatric Study Guidance at 15.

¹³⁷ See Opposition Comments at 16-24.

¹³⁸ 21 U.S.C. § 355(e); see also 21 C.F.R. § 314.150(a)(1).

health.”¹³⁹ In the Petition and in this Response, the Petitioners have provided extensive evidence that Mifeprex poses, under FDA’s definition, “a significant threat of danger to health, [and] creates a public health situation . . . that should be corrected immediately to prevent injury.”¹⁴⁰ Furthermore, an emergency or “crisis” situation is not required, but merely a “substantial likelihood that serious harm will be experienced during . . . any realistic projection of the administrative process.”¹⁴¹ In interpreting this definition, a court upheld an FDA decision similar to that which the Petitioners are requesting. Specifically, even though “respectable scientific authority [could] be found on both sides of this question”, and “much of the raw data used by the [Agency] in arriving at its conclusion had been available for some length of time,” these facts did not preclude FDA’s use of the data in finding an imminent hazard when “the magnitude of [the drug’s] risk was determined only after an extensive *re-evaluation of the data*.”¹⁴²

FDA’s authority is resolute and can be exercised immediately, notwithstanding any related issues regarding how the matter was initially raised (*e.g.*, a Citizen Petition), who exercised the authority (*e.g.*, HHS Secretary or FDA), and what actions follow it (*e.g.*, notice and hearing).¹⁴³ FDA should disregard the Sponsor’s attempt to redirect the Agency away from the substance of the Petition toward a focus on the administrative requirements of delegating authority, providing notice, and holding a hearing. Clearly, FDA’s suspension of the Mifeprex approval could occur during the pendency of any notice period or hearing which the Sponsor so forcefully claims to be entitled to under the FD&C Act, the APA and Constitutional due process provisions. Given the situation, the Petitioners are dismayed at the Sponsor’s insistence that its “property right to produce and market Mifeprex,”¹⁴⁴ outweighs any concern for the safety of the patients that the Sponsor is seeking to “treat.”

Furthermore, even if FDA finds that an imminent hazard does not exist in this case, FDA may still summarily withdraw approval of an NDA in certain circumstances. During its four-page discussion on notice and hearings, the Sponsor fails to mention that the FD&C Act’s “due notice and hearing” provision does not guarantee an NDA Sponsor a hearing, and also leaves FDA with discretion regarding the type of notice that is provided.¹⁴⁵ Rather, FDA may proceed by summary judgment to withdraw an NDA in certain circumstances – for example, when there

¹³⁹ See *id.*

¹⁴⁰ 21 C.F.R. § 2.5.

¹⁴¹ *Forsham v. Califano*, 442 F. Supp. 203, 208 (D.D.C. 1977) (citing *Environmental Defense Fund v. EPA*, 510 F.2d 1292, 1297 (D.C. Cir 1975)).

¹⁴² *Forsham v. Califano*, 442 F. Supp. 203, 209 (D.D.C. 1977) (emphasis added).

¹⁴³ *Forsham v. Califano*, 442 F. Supp. 203 (D.D.C. 1977) (on petition raised by a consumer health organization, the HHS Secretary referred the matter to FDA, which withdrew approval of a drug with notice but no formal hearing, based on a finding of imminent hazard to the public health).

¹⁴⁴ Opposition Comments at 18. When the Sponsor included misoprostol as part of the Mifeprex Regimen, it did not demonstrate any concern for the property rights of Searle over misoprostol.

¹⁴⁵ See *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 518, 520 (D.C. Cir. 1988) (“It is well settled that this [notice and hearing] provision does not guarantee the applicant a hearing in all circumstances.” and “The requirements of ‘due notice’ must depend upon the context of the agency’s action.”); *Brandenfels v. Heckler*, 716 F.2d 553, 555 (9th Cir. 1983) (“The FDA is authorized to satisfy its own notice requirements by providing holders of new drug applications with either general or specific notice of opportunity for hearing.”).

is no genuine and substantial issue of fact, when the applicant does not meet the minimum regulatory requirements, or when it appears conclusively from the applicant's pleadings that the applicant cannot succeed.¹⁴⁶

The Petitioners' request for administrative stay contains ample evidence to support a finding in this case of imminent hazard or the requisite basis for summary withdrawal. Millions of women are being misled to believe that the Mifeprex Regimen is safe, while in actuality neither the data submitted in the original NDA nor the subsequent marketing history can support a safety profile that justifies the continued marketing of the drug product. There is simply no legal basis to assert that FDA lacks the authority to grant the requested remedy of a "stay" (*i.e.*, suspension) of the NDA pending resolution of a formal NDA withdrawal process.

B. The Request for Administrative Stay Was Timely Filed.

An NDA is not a "static" document. Rather, it is a "living" document that is constantly being supplemented, updated, and reviewed by FDA.¹⁴⁷ Therefore, FDA is constantly making a "decision" to allow an NDA approval to stand in light of new information that is submitted to the Agency. Likewise, a drug's safety and efficacy profile and risk/benefit profile also require constant re-analysis by FDA. For example, over time "newer" medical evidence comes to light and adverse reactions are recorded in the patient population. FDA's approval decisions on NDAs are not "stuck in time." Instead, "FDA has an obligation to judge a drug's effectiveness by contemporary scientific standards. If those standards change to the extent that it is questionable whether a drug can be regarded as having been shown to be effective, FDA may under the act appropriately review the drug's status."¹⁴⁸

FDA's regulations state that a stay of action must be filed within 30 days of the "date of the *decision involved*" unless FDA permits a later filing for "good cause."¹⁴⁹ In this instance, the "decision involved" is FDA's decision to uphold the Mifeprex NDA and to *not* suspend the approval despite the influx of new information. This decision is ongoing. The Petitioners are requesting that FDA "stay" that decision and suspend the NDA approval immediately in response to the imminent hazard presented by the Mifeprex Regimen.

¹⁴⁶ See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 620-1 (1973) (withdrawing approval of NDA without a hearing based on lack of evidence negating "new drug" status); *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 518 (D.C. Cir. 1988) (withdrawing approval of NDA without a hearing based on failure to comply with current good manufacturing practices); *Cooper Laboratories, Inc. v. FDA*, 501 F.2d 772, 780 (D.C. Cir. 1974) (withdrawing approval of NDA without a hearing based on insufficient evidence of efficacy).

¹⁴⁷ See, *e.g.*, 21 C.F.R. §§ 314.70, 314.72, 314.80, 314.81. At the very least, the Sponsor of the Mifeprex NDA is required to submit an annual report to FDA each year. 21 C.F.R. § 314.81(b)(2). The Sponsor's misdirection on this matter is revealed by the fact that, under their interpretation of the "30 days" filing requirement, the Petitioners could "cure" the alleged timeliness defect by merely submitting the Petition within 30 days of any Mifeprex NDA Supplement or Annual Report.

¹⁴⁸ 50 Fed. Reg. 7452, 7488 (Feb. 22, 1985) (FDA's rejection of an industry suggestion, on withdrawal of approval of an application under 21 C.F.R. § 314.150, that FDA's conclusion concerning a drug product "should remain unchanged even if FDA later adopted new standards").

¹⁴⁹ 21 C.F.R. § 10.35(b) (emphasis added).

Even if the request were considered to be “untimely” from a technical perspective, FDA should nevertheless still grant the requested stay pursuant to either (1) the Agency’s “imminent hazard” authority under section 505(e), which contains no time limitation; or (2) the “good cause” exception of 21 C.F.R. § 10.35(b). In fact, the “imminent hazard” authority and the “good cause” exception were included in the statute and regulations for the very reasons outlined in the Petitioners’ request. Namely, these provisions allow FDA to move quickly to protect the public from unsafe drug products without being slowed by overly technical readings of the regulations. Additionally, if FDA deemed the request to be untimely filed, the Agency still may stay its action on the NDA on its own initiative *at any time*. In other words, if FDA determines that the Petition’s underlying request has merit, FDA may suspend approval and/or initiate withdrawal proceedings independent of the Petitioners’ request.

C. The Petitioners Comply with the Spirit and Letter of the Requirements for an Administrative Stay.

As supported by the original submission, the Petitioners’ request for an administrative stay meets all of the requirements of 21 C.F.R. § 10.35(e). In particular, the Petitioners have demonstrated irreparable harm to American women and an overwhelming public policy reason for removing the Mifeprex drug product from the market. The Petitioners’ request is clearly not frivolous, and is being pursued in good faith. In response, the Sponsor has raised minor technical challenges that obfuscate and mischaracterize the issues raised by the Petitioners. Despite the evidence contained in the Petition concerning the harm that Mifeprex is inflicting on American women, and the Petitioners’ direct interest as their physicians in speaking for these women, the Sponsor has alleged that there is insufficient injury to justify an administrative stay. Specifically, the Sponsor argued that the Petitioners are not the *actual* injured party.¹⁵⁰ Yet, that response is a mischaracterization of the Petitioners’ request. The Petition clearly stated that the Petitioners were seeking Agency action to prevent further injury to women seeking to terminate their pregnancies.¹⁵¹ The evidence submitted in the Petition and in this submission unequivocally demonstrates that women are being harmed by this drug product. In light of this fact, FDA is obliged to investigate whether the Mifeprex NDA approval should be suspended and ultimately withdrawn.

¹⁵⁰ See Opposition Comments at 21-22.

¹⁵¹ Just as the Petitioners have with their Petition, patient advocacy groups routinely utilize the Citizen Petition process to request that FDA overturn its safety and effectiveness decision for drug products and, ultimately, withdraw them from the market. See Letter to FDA from AIDS Healthcare Foundation, August 19, 2003 (Docket number not assigned), requesting market removal of Trizivir (abacavir sulfate/lamivudine/zidovudine) due to poor efficacy results in post-approval clinical studies letter; Docket No. 02P-1778, Citizen Petition from Public Citizen and Arizona Arthritis Center, March 28, 2002, requesting market removal of Arava (leflunomide) due to patient deaths and severe liver failure; Docket No. 02P-0120, Citizen Petition from Public Citizen, March 19, 2002, requesting market removal of Meridia (sibutramine) due to patient deaths related to cardiovascular adverse effects. Many of these Citizen Petitions are ultimately successful. See *e.g.*, Rezulin (troglitazone), banned March 2000 after a July 1998 Petition (Docket No. 98-0622); and Lotronex (alosetron HCl), banned November 2000 after an August 2000 Petition (Docket No. 00P-1499).

III. Conclusion.

For the foregoing reasons, the Petitioners respectfully request that FDA immediately suspend the approval of the NDA for Mifeprex and enter an administrative stay to halt any further distribution and marketing of Mifeprex until final Agency action is taken to withdraw the NDA approval for Mifeprex. For copies of any of the reference materials cited herein, please contact the undersigned.

Respectfully submitted,

Gary L. Yingling

Rebecca L. Dandeker

EXHIBIT 20

2011 FDA Supplemental Approval Letter to Danco Labs



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-014

SUPPLEMENT APPROVAL

Danco Laboratories, LLC

(b) (6)

P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX[®] (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

- a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
- b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 020687
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the [REDACTED] (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, [REDACTED] (b) (6)

Sincerely,

{See appended electronic signature page}

[REDACTED] (b) (6)

ENCLOSURES:

REMS Document
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011